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1° July 11, 1997

L26: Entry 2 of 4 File: USPT Mar 23, 1999

DOCUMENT-IDENTIFIER: US 5885580 A
TITLE: Anti-AIDS secretory recombinant BCG vaccine

Brief Summary Text (9):
The higher-order structures of the carrier proteins derived from the above-mentioned viruses have already been clarified. In the above-mentioned fusion proteins, the foreign antigen peptide has been inserted into the loop site which may become B cell epitope with ease and which exists on the molecular surface of the carrier protein.

Delivered Mol. Cell Biol Vol 11 1751-1753 1991 disulfide Cysteine - cysteine

SEKDEL KDEL

Nat II pJ414

P38 cells 16 aa 340 - 380 deleted

6083502 5980895

Intracellular retention sequences

Foreign heterologous non-native antigen

US-CL-CURRENT: 424/260.1; 424/183.1, 424/236.1, 435/69.1, 435/69.7, 435/71.3, 435/875, 530/356, 530/387.3, 530/391.7

INT-CL: [06] A61 K 39/104, C07 K 3/00

L12: Entry 4 of 16 File: USPT Jan 6, 1998

US-PAT-NO: 5705156
DOCUMENT-IDENTIFIER: US 5705156 A

TITLE: Psuedomonas exotoxins of low animal toxicity and high cytocidal activity

DATE-ISSUED: January 6, 1998

US-CL-CURRENT: 424/183.1; 424/192.1, 424/236.1, 424/260.1, 530/391.7

INT-CL: [06] A61 K 39/395, A61 K 39/00, A61 K 39/02, A61 K 39/108

L12: Entry 5 of 16 File: USPT Dec 9, 1997

US-PAT-NO: 5696237
DOCUMENT-IDENTIFIER: US 5696237 A
**** See image for Certificate of Correction ****

TITLE: Recombinant antibody-toxin fusion protein

DATE-ISSUED: December 9, 1997

US-CL-CURRENT: 530/387.3; 530/388.22, 530/391.7

INT-CL: [06] C07 K 16/46

L12: Entry 6 of 16 File: USPT Mar 4, 1997

US-PAT-NO: 5608039
DOCUMENT-IDENTIFIER: US 5608039 A

TITLE: Single chain B3 antibody fusion proteins and their uses

DATE-ISSUED: March 4, 1997

US-CL-CURRENT: 530/387.3; 435/69.1, 435/69.7, 435/91.1, 530/387.1, 530/387.5, 530/387.7, 530/388.1, 530/388.8, 530/390.5 , 530/866, 530/867, 536/23.53

INT-CL: [06] C12 N 15/62, A61 K 39/00, A61 K 51/10, C07 K 16/28

L12: Entry 7 of 16 File: USPT Feb 11, 1997

US-PAT-NO: 5602095
DOCUMENT-IDENTIFIER: US 5602095 A

TITLE: Recombinant pseudomonas exotoxin with increased activity

DATE-ISSUED: February 11, 1997

US-CL-CURRENT: 514/12; 424/192.1, 424/193.1, 424/236.1, 435/252.3, 435/252.33, 435/320.1, 435/69.1, 435/69.3, 435/69.7, 514/2, 530/350, 530/351, 530/403, 530/825, 930/200

INT-CL: [06] C07 K 14/21

L12: Entry 8 of 16 File: USPT Dec 24, 1996

US-PAT-NO: 5587455
DOCUMENT-IDENTIFIER: US 5587455 A

TITLE: Cytotoxic agent against specific virus infection

DATE-ISSUED: December 24, 1996

US-CL-CURRENT: 530/324; 530/350

INT-CL: [06] C07 K 14/21, C07 K 14/73

L12: Entry 9 of 16 File: USPT Apr 30, 1996

US-PAT-NO: 5512658
DOCUMENT-IDENTIFIER: US 5512658 A

TITLE: Pseudomonas exotoxins (PE) and conjugates thereof having lower animal toxicity with high cytocidal activity through substitution of positively charged amino acids

DATE-ISSUED: April 30, 1996

US-CL-CURRENT: 530/350; 424/183.1, 424/236.1, 424/260.1, 435/69.1, 435/69.7, 435/71.3, 435/875, 530/387.3, 530/391.7

INT-CL: [06] C12 N 15/31, C07 K 14/21, A61 K 39/04

L12: Entry 10 of 16 File: USPT Oct 17, 1995

US-PAT-NO: 5458878

DOCUMENT-IDENTIFIER: US 5458878 A

TITLE: P. exotoxin fusio proteins have COOHG220101al alterations which increase cytotoxicity

DATE-ISSUED: October 17, 1995

US-CL-CURRENT: 424/260.1; 424/279.1, 435/69.7, 530/387.3, 530/391.7

INT-CL: [06] A61 K 39/104, C07 K 3/00, C07 K 15/28, C12 P 21/08

L12: Entry 11 of 16 File: USPT Jul 12, 1994

US-PAT-NO: 5328984
DOCUMENT-IDENTIFIER: US 5328984 A
**** See image for Certificate of Correction ****

TITLE: Recombinant chimeric proteins deliverable across cellular membranes into cytosol of target cells

DATE-ISSUED: July 12, 1994

US-CL-CURRENT: 424/134.1; 435/69.7, 530/350, 530/387.3, 530/399, 530/402, 536/23.4

INT-CL: [05] C07K 13/00, C07K 15/04, A61K 37/02

L12: Entry 12 of 16 File: USPT Jan 21, 1992

US-PAT-NO: 5082927
DOCUMENT-IDENTIFIER: US 5082927 A

TITLE: Selectively cytotoxic IL-4-PE40 fusion protein

DATE-ISSUED: January 21, 1992

US-CL-CURRENT: 530/351; 424/192.1, 424/85.1, 424/85.2, 435/4, 435/69.5, 435/69.52, 435/71.3, 514/2, 514/8, 530/402, 530/403, 530/404, 530/405, 530/406, 530/820, 530/825

INT-CL: [05] C07K 15/00, A61K 37/02, A61K 39/104

L12: Entry 13 of 16 File: USPT Sep 18, 1990

US-PAT-NO: 4958009
DOCUMENT-IDENTIFIER: US 4958009 A

TITLE: Anti-human ovarian cancer immunotoxins and methods of use thereof

DATE-ISSUED: September 18, 1990

US-CL-CURRENT: 424/183.1; 424/155.1, 424/156.1, 424/804, 424/807, 514/885, 530/388.8, 530/388.85, 530/391.7, 530/808, 530/864

INT-CL: [05] C07K 15/12, A61K 39/00

L12: Entry 14 of 16 File: USPT Jan 9, 1990

US-PAT-NO: 4892827
DOCUMENT-IDENTIFIER: US 4892827 A

TITLE: Recombinant pseudomonas exotoxins: construction of an active immunotoxin with low side effects

DATE-ISSUED: January 9, 1990

US-CL-CURRENT: 435/193; 424/183.1, 424/94.5, 435/69.4, 435/69.52, 435/69.6, 435/69.7, 514/12, 514/2, 514/6, 530/350, 530/351, 530/370, 530/391.7, 530/395, 530/396

INT-CL: [04] C12P 21/00, C12P 21/02, C12N 9/10, A61K 34/00

L12: Entry 15 of 16 File: USPT Feb 21, 1989

US-PAT-NO: 4806494
DOCUMENT-IDENTIFIER: US 4806494 A

TITLE: Monoclonal antibody against ovarian cancer cells (OVB-3)

DATE-ISSUED: February 21, 1989

US-CL-CURRENT: 530/388.8; 424/179.1, 436/518, 436/519, 436/548, 514/2, 530/388.2, 530/391.7, 530/391.9

INT-CL: [04] G01N 33/53, G01N 33/543, A61K 39/00, A61K 45/02

L12: Entry 16 of 16 File: USPT Oct 8, 1985

US-PAT-NO: 4545985
DOCUMENT-IDENTIFIER: US 4545985 A

TITLE: Pseudomonas exotoxin conjugate immunotoxins

DATE-ISSUED: October 8, 1985

US-CL-CURRENT: 424/180.1; 424/179.1, 514/2, 514/6, 530/388.22, 530/388.23, 530/391.9, 530/404, 530/414, 530/806, 530/807 , 530/825, 530/826, 530/828

INT-CL: [04] A61K 39/00, A61K 39/02, A61K 37/00, A23J 1/06

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L15: Entry 2 of 24 File: USPT Jul 30, 2002

DOCUMENT-IDENTIFIER: US 6426075 B1
TITLE: Protease-activatable pseudomonas exotoxin A-like proproteins

CLAIMS:

1. A protease-activatable Pseudomonas exotoxin A-like ("PE-like") proprotein comprising: (a) a cell recognition domain that binds to an exterior surface of a targeted cell; (b) a modified PE translocation domain comprising an amino acid sequence with 80% or greater sequence identity to amino acids 280 to 344 of SEQ ID NO:2 and which effects translocation to a cell cytosol upon proteolytic cleavage, wherein the translocation domain comprises a cysteine-cysteine loop that comprises a protease activatable sequence cleavable by a protease and wherein the protease activatable sequence is refractory to cleavage by furin when incubated with furin at a 1:10 enzyme:substrate molar ratio at 25.degree. C. for 16 hour; (c) a cytotoxicity domain comprising an amino acid sequence with 80% or greater sequence identity to amino acids 400 to 613 of SEQ ID NO:2, the cytotoxicity domain having ADP-ribosylating activity; and (d) an endoplasmic reticulum ("ER") retention sequence.

13. A composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a protease-specific Pseudomonas exotoxin A-like ("PE-like") proprotein comprising: (a) a cell recognition domain that binds to an exterior surface of a targeted cell; (b) a modified PE translocation domain comprising an amino acid sequence with 80% or greater sequence identity to amino acids 280 to 344 of SEQ ID NO:2 and which effects translocation to a cell cytosol upon proteolytic cleavage, wherein the translocation domain comprises a cysteine-cysteine loop that comprises a protease activatable sequence cleavable by a protease and wherein the protease activatable sequence is substantially un-activatable by fibrin when incubated with furin at a 1:10 enzyme:substrate molar ratio at 25.degree. C. for 16 hours; (c) a cytotoxicity domain comprising an amino acid sequence with 80% or greater sequence identity to amino acids 400 to 613 of SEQ WD NO:2, the cytotoxicity domain having ADP-ribosylating activity; and (d) an endoplasmic reticulum ("ER") retention sequence.

16. A method for killing a cancer cell comprising contacting the cell with a protease-specific Pseudomonas exotoxin A-like ("PE-like") proprotein comprising: (a) a cell recognition domain that binds to an exterior surface of a targeted cell; (b) a modified PE translocation domain comprising an amino acid sequence with 80% or greater sequence identity to amino acids 280 to 344 of SEQ ID NO:2 and which effects translocation to a cell cytosol upon proteolytic cleavage, wherein the translocation domain comprises a cysteine-cysteine loop that comprises a protease activatable sequence cleavable by a protease and wherein the protease activatable sequence cysteine-cysteine loop is substantially un-activatable by furin when incubated with furin at a 1:10 enzyme:substrate molar ratio at 25.degree. C. for 16 hours; (c) a cytotoxicity domain comprising an amino acid sequence with 80% or greater sequence identity to amino acids 400 to 613 of SEQ ID NO:2, the cytotoxicity

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L14: Entry 16 of 36 File: USPT Feb 8, 2000

DOCUMENT-IDENTIFIER: US 6022950 A
**** See image for Certificate of Correction ****
TITLE: Hybrid molecules having translocation region and cell-binding region

CLAIMS:

1. A hybrid molecule comprising a first part, a second part, and a third part connected by covalent bonds,

(a) wherein said first part comprises a portion of the binding domain of a cell-binding ligand effective to cause said hybrid molecule to bind to a cell of an animal;

(b) wherein said second part comprises a portion of a translocation domain of a naturally occurring protein which translocates said third part across the cytoplasmic membrane into the cytosol of the cell; and

(c) wherein said third part comprises a chemical entity to be introduced into the cell, wherein each of said first part and said third part is non-native with respect to said naturally occurring protein, and further wherein said covalent bond connecting said second part and said third part is a cleavable bond, provided that when said second part comprises a portion of a translocation domain of Pseudomonas exotoxin, said third part is not a polypeptide.

9. The hybrid molecule of claim 2, wherein said first part comprises the binding domain of said cell-binding polypeptide ligand.

14. The hybrid molecule of claim 2, wherein said first part comprises a portion of the binding domain of a polypeptide toxin.

34. A hybrid molecule comprising a first part, a second part and a third part connected by covalent bonds,

(a) wherein said first part comprises a portion of the binding domain of a cell-binding polypeptide ligand effective to cause said hybrid protein to bind to a cell of an animal;

(b) wherein said second part comprises a portion of the translocation domain of diphtheria toxin which translocates said third part across the cytoplasmic membrane and into the cytosol of the cell; and

(c) wherein said third part comprises a chemical entity to be introduced into the cell, wherein said chemical entity and said first part are non-native with respect to said diphtheria toxin, and further wherein said covalent bond connecting said second part and said third part is a cleavable bond.

35. The hybrid molecule of claim 34, wherein said first part comprises a portion of the binding domain of

interleukin II effective to cause said hybrid molecule to bind to an interleukin II receptor-bearing cell.

36. The hybrid molecule of claim 34, wherein said first part comprises a portion of the binding domain of EGF.

49. A hybrid molecule comprising a first part, a second part, and a third part connected by covalent bonds,

(a) wherein said first part comprises a portion of the binding domain of a cell-binding polypeptide ligand effective to cause said hybrid protein to bind to a cell of an animal;

(b) wherein said second part comprises a portion of a translocation domain of Shiga-like toxin which translocates said third part across the cytoplasmic membrane into the cytosol of the cell; and

(c) wherein said third part comprises an enzymatically active domain of Shiga-like toxin.

domain having ADP-ribosylating activity; and (d) an endoplasmic reticulum ("ER") retention sequence.

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L15: Entry 7 of 24 File: USPT Apr 17, 2001

DOCUMENT-IDENTIFIER: US 6217881 B1
TITLE: Antigenic modification of HCG polypeptides

Tetanus toxoid ingpec

CLAIMS:

1. A vaccine composition for provoking the formation of antibodies to human chorionic gonadotropin comprising a peptide having an amino acid sequence of Cys-Pro-Thr-Nle-Asp-Arg-Val-Leu-Gln-Gly-Val-Leu-Pro-Ala-Val-Pro-Gln-Val-Va l-Cys, with a disulfide bridge linking the terminal cysteine amino acids to form a loop; said peptide is conjugated to a carrier; and a vehicle.

3. A vaccine composition for provoking the formation of antibodies to human chorionic gonadotropin comprising a peptide having an amino acid sequence of Cys-Pro-Ser-Nle-Asp-Arg-Val-Leu-Gln-Gly-Val-Leu-Pro-Ala-Val-Pro-Asn-Leu-Le u-Cys with a disulfide bridge linking the terminal cysteine amino acids to form a loop; said peptide is conjugated to a carrier; and a vehicle.

4. A vaccine composition for provoking the formation of antibodies to human chorionic gonadotropin comprising a peptide having an amino acid sequence Cys-Pro-Gly-Gly-Gly-Arg-Val-Leu-Gln-Gly-Val-Leu-Pro-Ala-Val-Pro-Thr-Val-Va l-Cys with a disulfide bridge linking the terminal cysteine amino acids to form a loop; said peptide is conjugated to a carrier; and a vehicle.

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L22: Entry 1 of 59 File: USPT Jun 10, 2003

DOCUMENT-IDENTIFIER: US 6576232 B1
TITLE: IL13 mutants

Other Reference Publication (33):
Siegall et al., "Functional Analysis of Domains II, Ib, and III of Pseudomonas Exotoxin," J. Biol.Chem., 264:14256-142610 (1989).

The Canadian and Korean ExPASy sites, **ca.expasy.org** and **kr.expasy.org**, are temporarily not available.

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NiceProt View of TrEMBL: Q91X67

Printer-friendly view | Quick BlastP search

[Entry info] [Name and origin] [References] [Comments] [Cross-references] [Keywords] [Features] [Sequence] [Tools]

Note: most headings are clickable, even if they don't appear as links. They link to the user manual or other documents.

Entry information

Entry name	**Q91X67**
Primary accession number	**Q91X67**
Secondary accession numbers	None
Entered in TrEMBL in	Release 19, December 2001
Sequence was last modified in	Release 19, December 2001
Annotations were last modified in	Release 25, September 2003

Name and origin of the protein

Protein name	**Similar to KDEL (Lys-Asp-Glu-Leu) endoplasmic reticulum protein retention receptor 3**
Synonym	**ER lumen protein retaining receptor**
Gene name	**KDELR3** or **AI173274**
From	Mus musculus (Mouse) [TaxID: 10090]
Taxonomy	Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Rodentia; Sciurognathi; Muridae; Murinae; Mus.

References

[1]	SEQUENCE FROM NUCLEIC ACID. **TISSUE**=Salivary gland; Strausberg R.; Submitted (JUL-2001) to the EMBL/GenBank/DDBJ databases.

Comments

- ***FUNCTION***: Required for the retention of luminal endoplasmic reticulum proteins, determines the specificity of the luminal ER protein retention system. Also required for normal vesicular traffic through the Golgi *(By similarity)*.
- ***SUBCELLULAR LOCATION***: Integral membrane protein *(By similarity)*.
- ***SIMILARITY***: BELONGS TO THE ERD2 FAMILY.

Cross-references

EMBL	BC011472; [EMBL / GenBank / DDBJ] AAH11472.1; -. [CoDingSequence]
MGD	MGI:2145953; Kdelr3.
GeneLynx	KDELR3; Mus musculus.
GO	GO:0005783; Cellular component: endoplasmic reticulum *(inferred from electronic annotation).* GO:0016021; Cellular component: integral to membrane *(inferred from electronic annotation).* GO:0008565; Molecular function: protein transporter activity *(inferred from electronic annotation).* GO:0004872; Molecular function: receptor activity *(inferred from electronic annotation).* GO:0006886; Biological process: intracellular protein transport *(inferred from electronic annotation).*
SOURCE	KDELR3; Mus musculus.
Ensembl	Q91X67; Mus musculus. [Entry / Contig view]
InterPro	IPR000133; ERret_receptor. Graphical view of domain structure.
Pfam	PF00810; ER_lumen_recept; 1.
PRINTS	PR00660; ERLUMENR.
ProDom	PD005774; ERret_receptor; 1. [Domain structure / List of seq. sharing at least 1 domain]
PROSITE	PS00951; ER_LUMEN_RECEPTOR_1; 1. PS00952; ER_LUMEN_RECEPTOR_2; 1.
HOVERGEN	[Family / Alignment / Tree]
ProtoMap	Q91X67.
PRESAGE	Q91X67.
ModBase	Q91X67.
SWISS-2DPAGE	Get region on 2D PAGE.

Keywords

Endoplasmic reticulum; Protein transport; Receptor; Transmembrane; Transport.

Features

None

Sequence information

Length: **214** AA	Molecular weight: **25107 Da**	CRC64: **2543B3D81BA9648D** [This is a checksum on the sequence]

```
         10          20          30          40          50          60
          |           |           |           |           |           |
MNVFRILGDL SHLLAMILLL VKIWRSKSCA GISGKSQILF ALVFTTRYLD LFSNFISIYN

         70          80          90         100         110         120
          |           |           |           |           |           |
TVMKVVFLLC AYVTVYMIYW KFRKTFDIEN DTFRLEFLLV PVTGLSFLVN YSYTPMEVLW

        130         140         150         160         170         180
          |           |           |           |           |           |
TFSIYLESVA ILPQLFMISK PGEAETITTH YLFFLGLYRL LYLANWIRRY QTENFYDQIS

        190         200         210
          |           |           |
VVSGVVQTIF YCDFFYLYVT KVLKGKKLSL PVPV
```

Q91X67 in FASTA format

View entry in original TrEMBL format
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BLAST — BLAST submission on ExPASy/SIB or at NCBI (USA)

Sequence analysis tools: ProtParam, ProtScale, Compute pI/Mw, PeptideMass, PeptideCutter, Dotlet (Java)

ScanProsite, MotifScan

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The Canadian and Korean ExPASy sites, **ca.expasy.org** and **kr.expasy.org**, are temporarily not available.

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[Entry info] [Name and origin] [References] [Comments] [Cross-references] [Keywords] [Features] [Sequence] [Tools]

Note: most headings are clickable, even if they don't appear as links. They link to the user manual or other documents.

Entry information

Entry name	**Q96H29**
Primary accession number	**Q96H29**
Secondary accession numbers	None
Entered in TrEMBL in	Release 19, December 2001
Sequence was last modified in	Release 19, December 2001
Annotations were last modified in	Release 24, June 2003

Name and origin of the protein

Protein name	**Similar to KDEL (Lys-Asp-Glu-Leu) endoplasmic reticulum protein retention receptor 1**
Synonym	**ER lumen protein retaining receptor**
Gene name	None
From	Homo sapiens (Human) [TaxID: 9606]
Taxonomy	Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.

References

[1] SEQUENCE FROM NUCLEIC ACID.
TISSUE=Muscle;
Strausberg R.;
Submitted (MAY-2001) to the EMBL/GenBank/DDBJ databases.

Comments

- ***FUNCTION***: Required for the retention of luminal endoplasmic reticulum proteins, determines the specificity of the luminal ER protein retention system. Also required for normal vesicular traffic through the Golgi *(By similarity)*.
- ***SUBCELLULAR LOCATION***: Integral membrane protein *(By similarity)*.
- ***SIMILARITY***: BELONGS TO THE ERD2 FAMILY.

Cross-references

EMBL	BC008958; AAH08958.1; -. [EMBL / GenBank / DDBJ] [CoDingSequence]
GO	GO:0005783; Cellular component: endoplasmic reticulum *(inferred from electronic annotation).* GO:0016021; Cellular component: integral to membrane *(inferred from electronic annotation).* GO:0008565; Molecular function: protein transporter activity *(inferred from electronic annotation).* GO:0004872; Molecular function: receptor activity *(inferred from electronic annotation).* GO:0006886; Biological process: intracellular protein transport *(inferred from electronic annotation).*
Ensembl	Q96H29; Homo sapiens. [Entry / Contig view]
InterPro	IPR000133; ERret_receptor. Graphical view of domain structure.
Pfam	PF00810; ER_lumen_recept; 1.
PRINTS	PR00660; ERLUMENR.
ProDom	PD005774; ERret_receptor; 1. [Domain structure / List of seq. sharing at least 1 domain]
PROSITE	PS00951; ER_LUMEN_RECEPTOR_1; 1. PS00952; ER_LUMEN_RECEPTOR_2; 1.
HOVERGEN	[Family / Alignment / Tree]
ProtoMap	Q96H29.
PRESAGE	Q96H29.
ModBase	Q96H29.
SWISS-2DPAGE	Get region on 2D PAGE.

Keywords

Endoplasmic reticulum; **Protein transport**; **Receptor**; **Transmembrane**; **Transport**.

Features

None

Sequence information

Length: 190 AA	Molecular weight: 21912 Da	CRC64: 7266AFDD4137A009 [This is a checksum on the sequence]

```
         10         20         30         40         50         60
          |          |          |          |          |          |
MNLFRFLGDL SHLLAIILLL LKIWKSRSCA GISGKSQVLF AVVFTARYLD LFTNYISLYN

         70         80         90        100        110        120
          |          |          |          |          |          |
TCMKVVYIAC SFTTVWLIYS KFKATYDGNH DTFRVEFLVV PTAILAFLVN HDFTPLEILW

        130        140        150        160        170        180
          |          |          |          |          |          |
TFSIYLESVA ILPQLFMVSK TGEAETITSH YLFVVFCLLD KKKKSFHSLV FDSDDSFFFY

        190
          |
SVAPIFIKCF
```

Q96H29 in FASTA format

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Request for annotation of this TrEMBL entry

BLAST BLAST submission on ExPASy/SIB or at NCBI (USA)

Sequence analysis tools: ProtParam, ProtScale, Compute pI/Mw, PeptideMass, PeptideCutter, Dotlet (Java)

ScanProsite, MotifScan

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The Canadian and Korean ExPASy sites, **ca.expasy.org** and **kr.expasy.org**, are temporarily not available.

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Search in Swiss-Prot and TrEMBL for: kdel

Swiss-Prot Release 41.18 of 25-Jul-2003
TrEMBL Release 24.5 of 25-Jul-2003

- Number of sequences found in Swiss-Prot$_{(6)}$ and TrEMBL$_{(14)}$: **20**
- Note that the selected sequences can be saved to a file to be later retrieved; to do so, go to the bottom of this page.
- For more directed searches, you can use the Sequence Retrieval System SRS.

Search in Swiss-Prot: There are matches to 6 out of 131945 entries

ER21_BOVIN (**P33946**)
ER lumen protein retaining receptor 1 (KDEL receptor 1) (P23). {GENE: KDELR1 OR KDELR} - Bos taurus (Bovine)

ER21_HUMAN (**P24390**)
ER lumen protein retaining receptor 1 (KDEL receptor 1). {GENE: KDELR1 OR ERD2.1} - Homo sapiens (Human)
ER22_HUMAN (**P33947**)
ER lumen protein retaining receptor 2 (KDEL receptor 2) (ELP-1). {GENE: KDELR2 OR ERD2.2} - Homo sapiens (Human)
ER23_HUMAN (**O43731**)
ER lumen protein retaining receptor 3 (KDEL receptor 3). {GENE: KDELR3} - Homo sapiens (Human)
ERD2_DROME (**O76767**)
ER lumen protein retaining receptor. {GENE: KDELR OR ERD2 OR CG5183} - Drosophila melanogaster (Fruit fly)
ERD2_XENLA (**O42580**)
ER lumen protein retaining receptor (KDEL receptor). {GENE: ERD2} - Xenopus laevis (African clawed frog)

Search in TrEMBL: There are matches to 14 out of 941701 entries

Q86JE5
Similar to Homo sapiens (Human). ER lumen protein retaining receptor 1 (KDEL receptor 1) - Dictyostelium discoideum (Slime mold)
Q8BPU6
KDEL containing protein 1 {GENE:KDEL1} - Mus musculus (Mouse)
Q8C528
KDEL containing protein 1 {GENE:KDEL1} - Mus musculus (Mouse)
Q8I7E2
KDEL receptor {GENE:ERD2} - Ciona intestinalis
Q8R1L4
Expressed sequence AI173274 (ER lumen protein retaining receptor) {GENE:KDELR3 OR AI173274} - Mus musculus (Mouse)
Q8R591
Similar to KDEL containing protein 1 {GENE:KDEL1} - Mus musculus

(Mouse)

Q8SRM5

ER lumen protein retaining receptor (KDEL receptor 2) {GENE:ECU06_1570} - Encephalitozoon cuniculi

Q91X67

Similar to KDEL (Lys-Asp-Glu-Leu) endoplasmic reticulum protein retention receptor 3 (ER lumen protein retaining receptor) {GENE:KDELR3 OR AI173274} - Mus musculus (Mouse)

Q96H29

Similar to KDEL (Lys-Asp-Glu-Leu) endoplasmic reticulum protein retention receptor 1 (ER lumen protein retaining receptor) - Homo sapiens (Human)

Q99JH8

Putative KDEL receptor (ER lumen protein retaining receptor) (KDEL endoplasmic reticulum protein retention receptor 1) {GENE:KDELR1 OR 8030486F04RIK OR ERD2.1} - Mus musculus (Mouse)

Q9CQM2

1110007A14Rik protein (Putative KDEL receptor) (RIKEN cDNA 1110007A14 gene) (ER lumen protein retaining receptor) {GENE:KDELR2 OR 1110007A14RIK OR ERD2.2} - Mus musculus (Mouse)

Q9D8P1

1810049A15Rik protein {GENE:KDEL1 OR 1810049A15RIK} - Mus musculus (Mouse)

Q9GLI7

KDEL receptor-like protein (Fragment) - Sus scrofa (Pig)

Q9JHP7

ER protein 58 (KDEL containing protein 1) {GENE:KDEL1 OR EP58} - Mus musculus (Mouse)

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Please do NOT use any boolean operators (and, or, etc.)

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WEST

updated search 7/03 VCP

Search Results - Record(s) 1 through 16 of 16 returned.

L12: Entry 1 of 16 File: USPT Dec 29, 1998

US-PAT-NO: 5854044
DOCUMENT-IDENTIFIER: US 5854044 A

TITLE: Recombinant pseudomonas exotoxin with increased activity

DATE-ISSUED: December 29, 1998

US-CL-CURRENT: 435/194; 530/324, 530/350, 530/351, 530/387.3, 530/387.7, 530/399

INT-CL: [06] C07 K 19/00, C12 N 9/12

L12: Entry 2 of 16 File: USPT Oct 13, 1998

US-PAT-NO: 5821238
DOCUMENT-IDENTIFIER: US 5821238 A

TITLE: Recombinant pseudomonas exotoxin with increased activity

DATE-ISSUED: October 13, 1998

US-CL-CURRENT: 424/134.1; 424/179.1, 424/183.1, 424/832, 435/69.7, 514/12, 530/350, 530/387.1, 530/387.3, 530/387.7, 530/391.7, 530/825

INT-CL: [06] A61 K 39/104, A61 K 38/43, C07 K 14/21, C12 P 21/02

L12: Entry 3 of 16 File: USPT Jan 6, 1998

US-PAT-NO: 5705163
DOCUMENT-IDENTIFIER: US 5705163 A
**** See image for Certificate of Correction ****

TITLE: Target-specific, cytotoxic, recombinant pseudomonas exotoxin

DATE-ISSUED: January 6, 1998

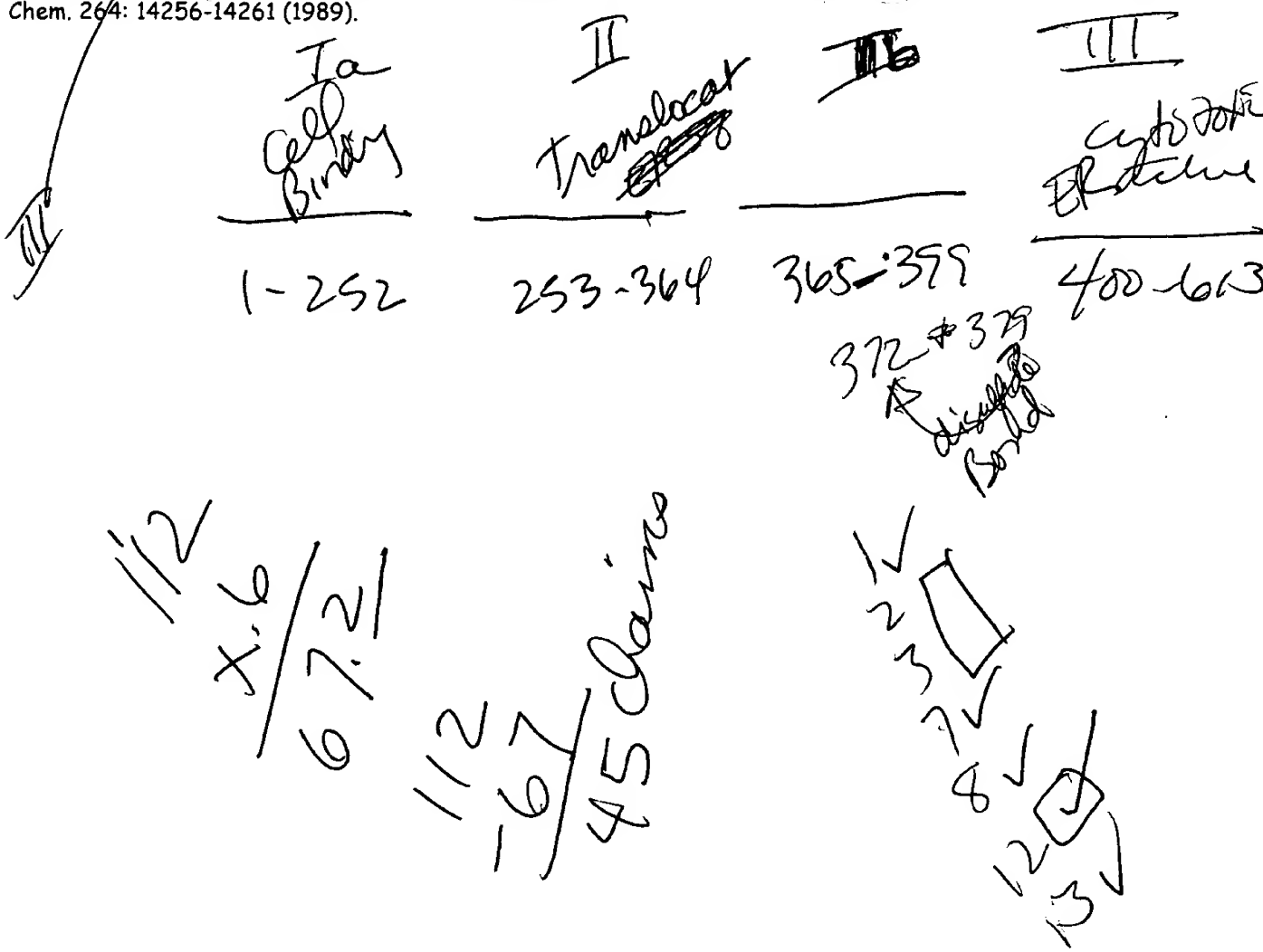
WEST

Generate Collection Print

L22: Entry 6 of 59 File: USPT Jan 28, 2003

DOCUMENT-IDENTIFIER: US 6512097 B1
TITLE: High affinity human antibodies to tumor antigens

Detailed Description Text (70):
The toxin contains three structural domains that act in concert to cause cytotoxicity. Domain Ia (amino acids 1-252) mediates cell binding. Domain II (amino acids 253-364) is responsible for translocation into the cytosol and domain m (amino acids 400-613) mediates ADP ribosylation of elongation factor 2, which inactivates the protein and causes cell death. The function of domain Ib (amino acids 365-399) remains undefined, although a large part of it, amino acids 365-380, can be deleted without loss of cytotoxicity. See Siegall et al., J. Biol. Chem. 264: 14256-14261 (1989).



NiceProt View of Swiss-Prot: P11439

Printer-friendly view | Quick BlastP search

[Entry info] [Name and origin] [References] [Comments] [Cross-references] [Keywords] [Features] [Sequence] [Tools]

Note: most headings are clickable, even if they don't appear as links. They link to the user manual or other documents.

Entry information

Entry name	**TOXA_PSEAE**
Primary accession number	**P11439**
Secondary accession number	Q9I4I7
Entered in Swiss-Prot in	Release 12, October 1989
Sequence was last modified in	Release 40, October 2001
Annotations were last modified in	Release 42, September 2003

Name and origin of the protein

Protein name	**Exotoxin A [Precursor]**
Synonyms	**NAD-dependent ADP-ribosyltransferase** **EC 2.4.2.-**
Gene name	**ETA** or **PA1148**
From	Pseudomonas aeruginosa [TaxID: 287]
Taxonomy	Bacteria; Proteobacteria; Gammaproteobacteria; Pseudomonadales; Pseudomonadaceae; Pseudomonas.

References

[1] SEQUENCE FROM NUCLEIC ACID, AND SEQUENCE OF 26-53.
MEDLINE=84194063; PubMed=6201861; [NCBI, ExPASy, EBI, Israel, Japan]
Gray G.L., Smith D.H., Baldridge J.S., Harkins R.N., Vasil M.L., Chen E.Y., Heyneker H.L.;
"Cloning, nucleotide sequence, and expression in Escherichia coli of the exotoxin A structural gene of Pseudomonas aeruginosa.";
Proc. Natl. Acad. Sci. U.S.A. 81:2645-2649(1984).

[2] SEQUENCE FROM NUCLEIC ACID.
STRAIN=ATCC 15692 / PAO1;
MEDLINE=20437337; PubMed=10984043; [NCBI, ExPASy, EBI, Israel, Japan]
Stover C.K., Pham X.-Q.T., Erwin A.L., Mizoguchi S.D., Warrener P., Hickey M.J., Brinkman F.S.L., Hufnagle W.O., Kowalik D.J., Lagrou M., Garber R.L., Goltry L., Tolentino E., Westbrock-Wadman S., Yuan Y., Brody L.L., Coulter S.N., Folger K.R., Kas A., Larbig K., Lim R.M., Smith K.A., Spencer D.H., Wong G.K.-S., Wu Z., Paulsen I.T., Reizer J., Saier M.H., Hancock R.E.W.,

	Lory S., Olson M.V.; "Complete genome sequence of Pseudomonas aeruginosa PAO1, an opportunistic pathogen."; Nature 406:959-964(2000).
[3]	ACTIVE SITE. MEDLINE=87250491; PubMed=2885323; [NCBI, ExPASy, EBI, Israel, Japan] Carroll S.F., Collier R.J.; "Active site of Pseudomonas aeruginosa exotoxin A. Glutamic acid 553 is photolabeled by NAD and shows functional homology with glutamic acid 148 of diphtheria toxin."; J. Biol. Chem. 262:8707-8711(1987).
[4]	DOMAINS. MEDLINE=90375493; PubMed=2118903; [NCBI, ExPASy, EBI, Israel, Japan] Chaudhary V.K., Jinno Y., Galo M.G., Fitzgerald D., Pastan I.; "Mutagenesis of Pseudomonas exotoxin in identification of sequences responsible for the animal toxicity."; J. Biol. Chem. 265:16306-16310(1990).
[5]	DOMAINS. MEDLINE=91006124; PubMed=2170123; [NCBI, ExPASy, EBI, Israel, Japan] Bourdenet S., Vacheron M.-J., Guinand M., Michel G., Arminjon F.; "Biochemical and immunochemical studies of proteolytic fragments of exotoxin A from Pseudomonas aeruginosa."; Eur. J. Biochem. 192:379-385(1990).
[6]	DISULFIDE BOND. MEDLINE=20068844; PubMed=10600112; [NCBI, ExPASy, EBI, Israel, Japan] McKee M.L., FitzGerald D.J.; "Reduction of furin-nicked Pseudomonas exotoxin A: an unfolding story."; Biochemistry 38:16507-16513(1999).
[7]	X-RAY CRYSTALLOGRAPHY (3.0 ANGSTROMS) OF 424-638. MEDLINE=96016159; PubMed=7568123; [NCBI, ExPASy, EBI, Israel, Japan]

	Li M., Dyda F., Benhar I., Pastan I., Davies D.R.; "The crystal structure of Pseudomonas aeruginosa exotoxin domain III with nicotinamide and AMP: conformational differences with the intact exotoxin."; Proc. Natl. Acad. Sci. U.S.A. 92:9308-9312(1995).
[8]	X-RAY CRYSTALLOGRAPHY (2.3 ANGSTROMS) OF 424-638. MEDLINE=96293446; PubMed=8692916; [NCBI, ExPASy, EBI, Israel, Japan] Li M., Dyda F., Benhar I., Pastan I., Davies D.R.; "Crystal structure of the catalytic domain of Pseudomonas exotoxin A complexed with a nicotinamide adenine dinucleotide analog: implications for the activation process and for ADP ribosylation."; Proc. Natl. Acad. Sci. U.S.A. 93:6902-6906(1996).

Comments

- ***FUNCTION***: THIS TOXIN IS AN NAD-DEPENDENT ADP-RIBOSYLTRANSFERASE. IT CATALYZES THE TRANSFER OF THE ADP RIBOSYL MOIETY OF OXIDIZED NAD ONTO ELONGATION FACTOR 2 (EF-2) THUS ARRESTING PROTEIN SYNTHESIS.
- ***PTM***: THE 8 CYSTEINES PARTICIPATE IN INTRACHAIN DISULFIDE BONDS.
- ***SIMILARITY***: REGIONAL SEQUENCE SIMILARITY AT THE ACTIVE SITE WITH DIPHTHERIA TOXIN (DT).

Copyright

Cross-references

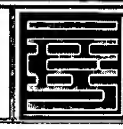
EMBL	K01397; AAB59097.1; [EMBL / GenBank / DDBJ] -. [CoDingSequence] AE004544; [EMBL / GenBank / DDBJ] AAG04537.1; -. [CoDingSequence]
PIR	A30347; A30347. C83503; C83503.
PDB	1AER; 10-JUN-96. [ExPASy / RCSB] 1DMA; 15-SEP-95. [ExPASy / RCSB] 1IKP; 12-DEC-01. [ExPASy / RCSB] 1IKQ; 12-DEC-01. [ExPASy / RCSB] Detailed list of linked structures.
SWISS-3DIMAGE	TOXA_PSEAE.
CMR	P11439; PA1148.
ProDom	[Domain structure / List of seq. sharing at least 1 domain]
HOBACGEN	[Family / Alignment / Tree]
BLOCKS	P11439.
ProtoNet	P11439.
ProtoMap	P11439.
PRESAGE	P11439.
DIP	P11439.
ModBase	P11439.
SWISS-2DPAGE	Get region on 2D PAGE.

Keywords

Toxin; **Signal**; **Transferase**; **Glycosyltransferase**; **NAD**; **3D-structure**; **Complete proteome**.

Features

 Feature table viewer

 Feature aligner

Key	From	To	Length	Description
SIGNAL	1	25	25	
CHAIN	26	638	613	EXOTOXIN A.

DOMAIN	26	277	252	IA (REQUIRED FOR TARGET CELL RECOGNITION).
DOMAIN	278	389	112	II (REQUIRED FOR TRANSLOCATION IN TARGET CELL CYTOPLASM).
DOMAIN	390	429	40	IB.
DOMAIN	430	638	209	III (REQUIRED FOR ADP-RIBOSYL ACTIVITY).
ACT_SITE	465	465		
ACT_SITE	578	578		INTERACT WITH NAD.
DISULFID	290	312		
CONFLICT	4	4		T -> I (IN REF. 1).
CONFLICT	22	22		F -> S (IN REF. 1).
CONFLICT	204	204		A -> T (IN REF. 1).
CONFLICT	389	389		S -> N (IN REF. 1).
CONFLICT	432	432		I -> V (IN REF. 1).
CONFLICT	540	540		G -> S (IN REF. 1).
STRAND	433	433	1	
TURN	436	437	2	
STRAND	440	440	1	
TURN	441	441	1	
HELIX	444	456	13	
TURN	457	458	2	
STRAND	459	467	9	
HELIX	469	476	8	
TURN	477	478	2	
TURN	490	491	2	
STRAND	494	497	4	
HELIX	500	504	5	
TURN	505	506	2	
STRAND	508	508	1	
TURN	514	515	2	
STRAND	520	520	1	
STRAND	522	529	8	
HELIX	530	535	6	
STRAND	536	538	3	

TURN	543	544	2
TURN	546	547	2
HELIX	548	556	9
TURN	557	557	1
STRAND	566	570	5
TURN	572	574	3
STRAND	577	581	5
HELIX	583	586	4
TURN	587	588	2
STRAND	590	593	4
TURN	600	601	2
TURN	603	604	2
HELIX	609	611	3
HELIX	614	617	4
TURN	618	619	2
STRAND	626	626	1

Sequence information

Length: **638 AA** [This is the length of the unprocessed precursor]	Molecular weight: **69284 Da** [This is the MW of the unprocessed precursor]	CRC64: **7B9AAD56A27C700A** [This is a checksum on the sequence]

```
        10          20          30          40          50          60
         |           |           |           |           |           |
MHLTPHWIPL VASLGLLAGG SFASAAEEAF DLWNECAKAC VLDLKDGVRS SRMSVDPAIA

        70          80          90         100         110         120
         |           |           |           |           |           |
DTNGQGVLHY SMVLEGGNDA LKLAIDNALS ITSDGLTIRL EGGVEPNKPV RYSYTRQARG

       130         140         150         160         170         180
         |           |           |           |           |           |
SWSLNWLVPI GHEKPSNIKV FIHELNAGNQ LSHMSPIYTI EMGDELLAKL ARDATFFVRA

       190         200         210         220         230         240
         |           |           |           |           |           |
HESNEMQPTL AISHAGVSVV MAQAQPRREK RWSEWASGKV LCLLDPLDGV YNYLAQQRCN

       250         260         270         280         290         300
         |           |           |           |           |           |
LDDTWEGKIY RVLAGNPAKH DLDIKPTVIS HRLHFPEGGS LAALTAHQAC HLPLETFTRH

       310         320         330         340         350         360
         |           |           |           |           |           |
RQPRGWEQLE QCGYPVQRLV ALYLAARLSW NQVDQVIRNA LASPGSGGDL GEAIREQPEQ

       370         380         390         400         410         420
         |           |           |           |           |           |
ARLALTLAAA ESERFVRQGT GNDEAGAASA DVVSLTCPVA AGECAGPADS GDALLERNYP

       430         440         450         460         470         480
         |           |           |           |           |           |
TGAEFLGDGG DISFSTRGTQ NWTVERLLQA HRQLEERGYV FVGYHGTFLE AAQSIVFGGV

       490         500         510         520         530         540
         |           |           |           |           |           |
RARSQDLDAI WRGFYIAGDP ALAYGYAQDQ EPDARGRIRN GALLRVYVPR SSLPGFYRTG

       550         560         570         580         590         600
         |           |           |           |           |           |
LTLAAPEAAG EVERLIGHPL PLRLDAITGP EEEGGRLETI LGWPLAERTV VIPSAIPTDP

       610         620         630
         |           |           |
RNVGGDLDPS SIPDKEQAIS ALPDYASQPG KPPREDLK
```

P11439 in FASTA format

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ScanProsite, MotifScan

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In case of problems, please contact us.

NCBI BLAST program reference [PMID:9254694]:
Altschul S.F., Madden T.L., Schäffer A.A., Zhang J., Zhang Z., Miller W., Lipman D.J. Gapped BLAST and PSI-BLAST: a new generation of protein database search programs. Nucleic Acids Res. 25:3389-3402(1997).

==========

Query length: 111 AA
Date run: 2003-07-28 17:24:24 UTC+0100 on sib-blast.unil.ch
Program: NCBI BLASTP 2.2.5 [Nov-16-2002]
Database: XXtremblnew; XXtrembl; XXswissprot
1,209,364 sequences; 390,881,785 total letters
Swiss-Prot Release 41.18 of 25-Jul-2003
TrEMBL Release 24.5 of 25-Jul-2003
TrEMBL_new of 25-Jul-2003

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List of potentially matching sequences

Send selected sequences to Clustal W (multiple alignment) Submit Query

Select up to...

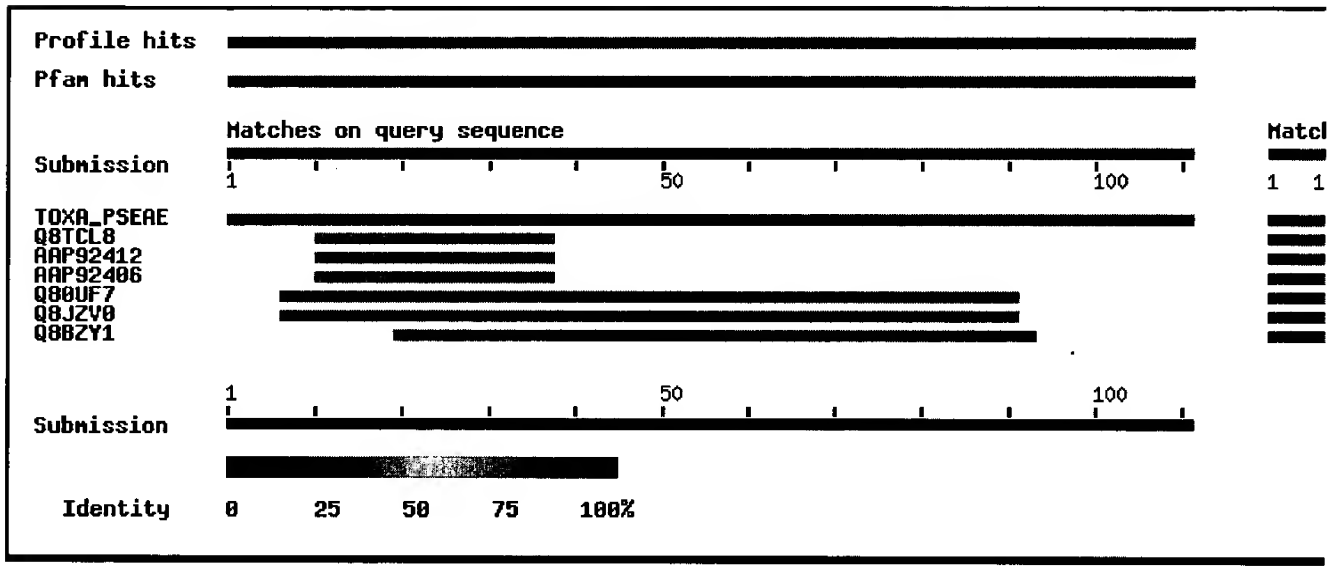
☐ Include query sequence

	Db	AC	Description	Score	E-value
☐	sp	P11439	TOXA_PSEAE Exotoxin A precursor (NAD-dependent ADP-rib...	231	1e-60
☐	tr	Q8TCL8	Hypothetical protein [DKFZP566B064] [Homo sapiens (Hum...	30	4.8
☐	tn	AAP92412	TAFA1 [Mus musculus (Mouse)]	30	4.8
☐	tn	AAP92406	TAFA1 [Homo sapiens (Human)]	30	4.8
☐	tr	Q80UF7	TICAM-1 [TICAM-1] [Mus musculus (Mouse)]	30	6.2
☐	tr	Q8JZV0	Hypothetical protein (Fragment) [AW046014] [Mus muscul...	30	6.2
☐	tr	Q8BZY1	Hypothetical type I antifreeze protein containing prot...	30	8.2

Graphical overview of the alignments

Click here to resubmit your query after masking regions matching PROSITE profiles or Pfam HMMs

(use ScanProsite for more details about PROSITE matches)



Alignments

sp P11439 TOXA_PSEAE **Exotoxin A precursor (NAD-dependent ADP-ribosyltransferase) (EC 2.4.2.-) [ETA] [Pseudomonas aeruginosa]** 638 AA align

Score = 231 bits (589), Expect = 1e-60
Identities = 111/111 (100%), Positives = 111/111 (100%)

```
Query: 1   AGNPAKHDLDIKPTVISHRLHFPEGGSLAALTAHQACHLPLETFTRHRQPRGWEQLEQCG 60
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Sbjct: 254 AGNPAKHDLDIKPTVISHRLHFPEGGSLAALTAHQACHLPLETFTRHRQPRGWEQLEQCG 313

Query: 61  YPVQRLVALYLAARLSWNQVDQVIRNALASPGSGGDLGEAIREQPEQARLA 111
           YPVQRLVALYLAARLSWNQVDQVIRNALASPGSGGDLGEAIREQPEQARLA
Sbjct: 314 YPVQRLVALYLAARLSWNQVDQVIRNALASPGSGGDLGEAIREQPEQARLA 364
```

tr Q8TCL8 **Hypothetical protein [DKFZP566B064] [Homo sapiens (Human)]** 133 AA
align

Score = 30.4 bits (67), Expect = 4.8
Identities = 11/28 (39%), Positives = 17/28 (60%)

```
Query: 11 IKPTVISHRLHFPEGGSLAALTAHQACH 38
          ++ T   H LH PEGG+   + AH+ C+
Sbjct: 27 LQHTFQQHHLHRPEGGTCEVIAAHRCCN 54
```

trnew AAP92412 **TAFA1 [Mus musculus (Mouse)]** 133 AA
align

Score = 30.4 bits (67), Expect = 4.8
Identities = 11/28 (39%), Positives = 17/28 (60%)

```
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          ++ T   H LH PEGG+   + AH+ C+
Sbjct: 27 LQHTFQQHHLHRPEGGTCEVIAAHRCCN 54
```

trnew AAP92406 **TAFA1 [Homo sapiens (Human)]** 133 AA
align

Score = 30.4 bits (67), Expect = 4.8
Identities = 11/28 (39%), Positives = 17/28 (60%)

```
Query: 11 IKPTVISHRLHFPEGGSLAALTAHQACH 38
          ++ T   H LH PEGG+   + AH+ C+
Sbjct: 27 LQHTFQQHHLHRPEGGTCEVIAAHRCCN 54
```

tr Q80UF7 **TICAM-1 [TICAM-1] [Mus musculus (Mouse)]** 732 AA
align

Score = 30.0 bits (66), Expect = 6.2
Identities = 26/99 (26%), Positives = 47/99 (47%), Gaps = 15/99 (15%)

```
Query: 7   HDLDIKPTVISHRLHFPEGGSLAALTAHQA-------CHLPLETFTRHRQPRGWEQLEQC 59
           H  +   ++ SH L   +  +LA L++H          C+ PL+T       P G ++ E+
Sbjct: 194 HSTNSTASLASH-LEISQSPTLAFLSSHHGTHGPSKLCNTPLDTQEPQLVPEGCQEPEEI 252

Query: 60  GYP--VQRLVALYLAARLSWNQV-----DQVIRNALASP 91
            +P  V+  V+L L   +S  +V        ++ +ALA+P
Sbjct: 253 SWPPSVETSVSLGLPHEISVPEVSPEEASPILPDALAAP 291
```

tr Q8JZV0 **Hypothetical protein (Fragment) [AW046014] [Mus musculus (Mouse)]** 798 AA align

Score = 30.0 bits (66), Expect = 6.2
Identities = 26/99 (26%), Positives = 47/99 (47%), Gaps = 15/99 (15%)

```
Query: 7   HDLDIKPTVISHRLHFPEGGSLAALTAHQA-------CHLPLETFTRHRQPRGWEQLEQC 59
           H  +    ++ SH L    +  +LA L++H          C+ PL+T       P G ++ E+
Sbjct: 260 HSTNSTASLASH-LEISQSPTLAFLSSHHGTHGPSKLCNTPLDTQEPQLVPEGCQEPEEI 318

Query: 60  GYP--VQRLVALYLAARLSWNQV-----DQVIRNALASP 91
            +P  V+  V+L L    +S  +V        ++ +ALA+P
Sbjct: 319 SWPPSVETSVSLGLPHEISVPEVSPEEASPILPDALAAP 357
```

tr Q8BZY1 **Hypothetical type I antifreeze protein containing protein (Fragment) [Mus musculus (Mouse)]** 578 AA align

Score = 29.6 bits (65), Expect = 8.2
Identities = 23/80 (28%), Positives = 32/80 (40%), Gaps = 8/80 (10%)

```
Query: 20  LHFPEGGSLAALTAHQAC------HLPLETFTRHRQPRGWEQLEQCGYPVQRLVALYLAA 73
           L  PEGG+ + +    +          L +E  T  R+     +  + C YP  R  A  LAA
Sbjct: 131 LRDPEGGATSPVDQEEEVDMDFLPQLSIEAMTVMRELTNLQLRKVCRYPSPRTCAAELAA 190

Query: 74  RLSWNQVDQVIRNALASPGS 93
               W  VD+        SP S
Sbjct: 191 --LWGNVDEGSNRGALSPSS 208
```

Database: XXtremblnew
Posted date: Jul 26, 2003 2:22 AM
Number of letters in database: 45,979,965
Number of sequences in database: 129,006

Database: XXtrembl
Posted date: Jul 26, 2003 2:12 AM
Number of letters in database: 292,266,813
Number of sequences in database: 941,996

Database: XXswissprot
Posted date: Jul 26, 2003 1:34 AM
Number of letters in database: 52,635,007
Number of sequences in database: 138,362

Lambda	K	H
0.319	0.135	0.419

Gapped

Lambda	K	H
0.267	0.0410	0.140

Matrix: BLOSUM62

```
Gap Penalties: Existence: 11, Extension: 1
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Number of extensions: 3491017
Number of successful extensions: 6106
Number of sequences better than 10.0: 7
Number of HSP's better than 10.0 without gapping: 4
Number of HSP's successfully gapped in prelim test: 3
Number of HSP's that attempted gapping in prelim test: 6102
Number of HSP's gapped (non-prelim): 7
length of query: 111
length of database: 390,881,785
effective HSP length: 87
effective length of query: 24
effective length of database: 285,667,117
effective search space: 6856010808
effective search space used: 6856010808
T: 11
A: 40
X1: 16 ( 7.4 bits)
X2: 38 (14.6 bits)
X3: 64 (24.7 bits)
S1: 41 (21.8 bits)
S2: 65 (29.6 bits)
```

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NCBI BLAST program reference [PMID:9254694]:
Altschul S.F., Madden T.L., Schäffer A.A., Zhang J., Zhang Z., Miller W., Lipman D.J. Gapped BLAST and PSI-BLAST: a new generation of protein database search programs. Nucleic Acids Res. 25:3389-3402(1997).

==========

Query length: 112 AA
Date run: 2003-07-28 17:26:48 UTC+0100 on sib-blast.unil.ch
Program: NCBI BLASTP 2.2.5 [Nov-16-2002]
Database: XXtremblnew; XXtrembl; XXswissprot
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Swiss-Prot Release 41.18 of 25-Jul-2003
TrEMBL Release 24.5 of 25-Jul-2003
TrEMBL_new of 25-Jul-2003

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List of potentially matching sequences

Send selected sequences to Clustal W (multiple alignment) Submit Query

Select up to...

☐ Include query sequence

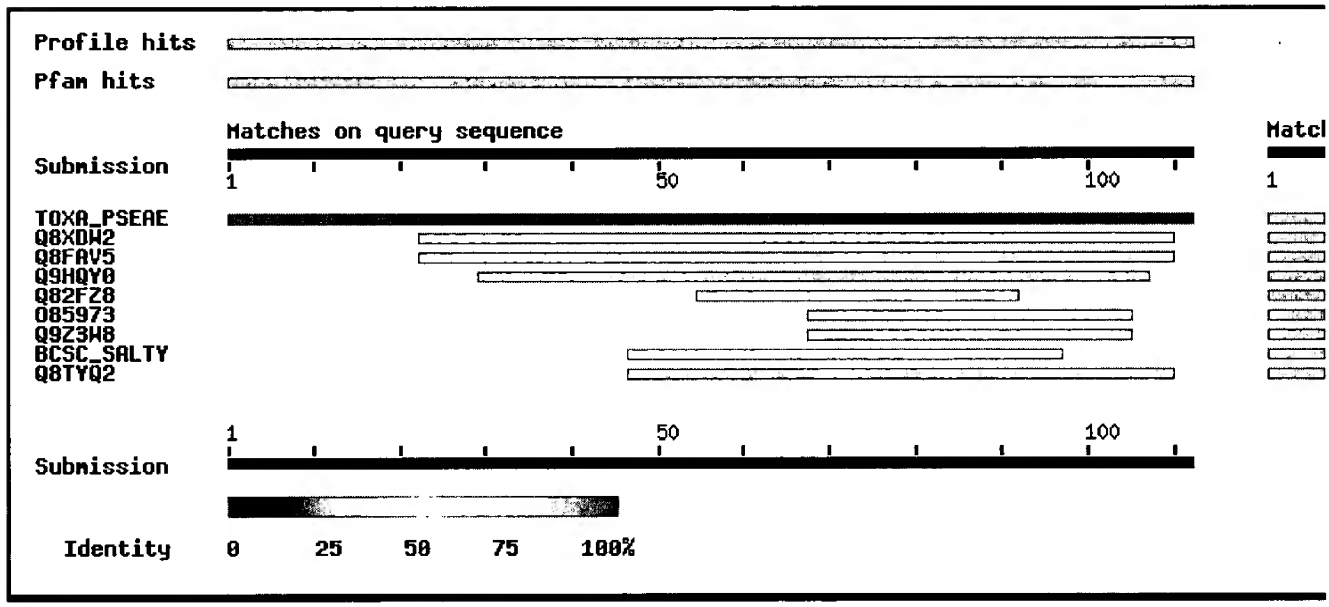
	Db	AC	Description	Score	E-value
☐	sp	P11439	TOXA_PSEAE Exotoxin A precursor (NAD-dependent ADP-rib...	226	3e-59
☐	tr	Q8XDW2	Phosphonate metabolism [PHNH] [Escherichia coli O157:H7]	33	0.96
☐	tr	Q8FAV5	PhnH protein [PHNH] [Escherichia coli O6]	32	2.1
☐	tr	Q9HQY0	Vng0954c [VNG0954C] [Halobacterium sp. (strain NRC-1 /...	31	2.8
☐	tr	Q82FZ8	Putative membrane protein [SAV4103] [Streptomyces aver...	31	3.6
☐	tr	O85973	Benzaldehyde dehydrogenase [XYLC] [Sphingomonas aromat...	31	3.6
☐	tr	Q9Z3W8	Benzaldehyde dehydrogenase [PHNN] [Sphingomonas chungb...	31	3.6
☐	sp	Q8ZLB8	BCSC_SALTY Cellulose synthase operon protein C [BCSC] ...	30	4.8

☐ tr Q8TYQ2 ATPase involved in chromosome partitioning [MK0240] [M... 30 8.1

Graphical overview of the alignments

Click here to resubmit your query after masking regions matching PROSITE profiles or Pfam HMMs

(use ScanProsite for more details about PROSITE matches)



Alignments

sp P11439 TOXA_PSEAE **Exotoxin A precursor (NAD-dependent ADP-ribosyltransferase) (EC 2.4.2.-) [ETA] [Pseudomonas aeruginosa]** 638 AA align

Score = 226 bits (577), Expect = 3e-59
Identities = 112/112 (100%), Positives = 112/112 (100%)

```
Query: 1   GGSLAALTAHQACHLPLETFTRHRQPRGWEQLEQCGYPVQRLVALYLAARLSWNQVDQVI 60
           GGSLAALTAHQACHLPLETFTRHRQPRGWEQLEQCGYPVQRLVALYLAARLSWNQVDQVI
Sbjct: 278 GGSLAALTAHQACHLPLETFTRHRQPRGWEQLEQCGYPVQRLVALYLAARLSWNQVDQVI 337

Query: 61  RNALASPGSGGDLGEAIREQPEQARLALTLAAAESERFVRQGTGNDEAGAAS 112
           RNALASPGSGGDLGEAIREQPEQARLALTLAAAESERFVRQGTGNDEAGAAS
Sbjct: 338 RNALASPGSGGDLGEAIREQPEQARLALTLAAAESERFVRQGTGNDEAGAAS 389
```

tr Q8XDW2 **Phosphonate metabolism [PHNH] [Escherichia coli O157:H7]** 194 AA
align

Score = 32.7 bits (73), Expect = 0.96
Identities = 32/96 (33%), Positives = 43/96 (44%), Gaps = 17/96 (17%)

```
Query: 23  HRQPRGWEQLEQCGYPVQRLVA-----LYLAARLSWNQVDQVIRNALASPGSGGDLGEAI 77
           H+  RGW+ L       V   +A      ++LAA LS + V Q +R     +P          +
Sbjct: 35  HQLKRGWQPLNIATTSVLLTLADNDTPVWLAAPLSNDIVSQSLRFHTNAP---------L 85

Query: 78  REQPEQARLALTLAAAESERFVRQGTGN---DEAGA 110
             QPEQA  A+T  A  SE+     TG     EAGA
Sbjct: 86  VSQPEQATFAVTDEAISSEQLNALSTGTAVAPEAGA 121
```

tr Q8FAV5 **PhnH protein [PHNH] [Escherichia coli O6]** 194 AA
align

Score = 31.6 bits (70), Expect = 2.1
Identities = 31/96 (32%), Positives = 44/96 (45%), Gaps = 17/96 (17%)

```
Query: 23  HRQPRGWEQLEQCGYPVQRLVA-----LYLAARLSWNQVDQVIRNALASPGSGGDLGEAI 77
           H+  RGW+ L       V   +A      ++LAA LS + V+Q +R     +P          +
Sbjct: 35  HQLKRGWQPLNIATTSVLLTLADNDTPVWLAAPLSNDIVNQSLRFHTNAP---------L 85

Query: 78  REQPEQARLALTLAAAESERFVRQGTGN---DEAGA 110
             QP+QA  A+T  A  SE+     TG     EAGA
Sbjct: 86  VNQPKQATFAVTDEAISSEQLNALSTGTAVAPEAGA 121
```

tr Q9HQY0 **Vng0954c [VNG0954C] [Halobacterium sp. (strain NRC-1 / ATCC 700922 / JCM 11081)]** 504 AA
align

Score = 31.2 bits (69), Expect = 2.8
Identities = 24/83 (28%), Positives = 35/83 (42%), Gaps = 5/83 (6%)

```
Query: 30  EQLEQCGYPVQRLVALYLAARLSWNQ-VDQVIRNALASPGSGGD----LGEAIREQPEQA 84
           E +E     V++L+ +Y        N  VD V  NA    PG GGD       E    +  E
Sbjct: 117 ESVEDVEENVRKLLEIYEMVTRGVNPFVDDVDPNAAGGPGGGGDSFGLFDEDEEDSDETG 176

Query: 85  RLALTLAAAESERFVRQGTGNDE 107
            L   +A AE++ F       +D+
Sbjct: 177 DLDTDVAEAEADEFFEDDAFDDD 199
```

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L6: Entry 66 of 67 File: USPT Apr 2, 1996

DOCUMENT-IDENTIFIER: US 5503829 A
TITLE: Recombinant mutants for inducing specific immune responses

Brief Summary Text (11):
Class I MHC is found on virtually all nucleated cells. Class I MHC generally associate with endogenously synthesized T epitopes for presentation to the cell mediated immune system. As this association of class I MHC to specific antigen occurs in the endoplasmic reticulum, antigens that are internalized by an antigen presenting cell via the endocytotic pathway will generally not become associated with class I MHC. The association of a specific T epitope with class I MHC and incorporation of the antigen-MHC class I complex on the surface of a cell stimulates specific cytotoxic T lymphocytes (CTL). The stimulated cytotoxic T lymphocytes can then kill the cell expressing the antigen-MHC complex by granule exocytosis of a membrane pore forming protein that causes cell lysis and secretion of a cell toxin that activates DNA degrading enzymes. However, the activation of the CTL cells also requires the activation of T helper cells in certain cases.

Brief Summary Text (12):
The other major class of MHC proteins is class II MHC. Class II MHC are also transmembrane proteins. Like class I MHC, class II MHC comprises two polypeptide chains and includes a polymorphic peptide binding region, an immunoglobulin-like region, a transmembrane region and a cytoplasmic domain. However, unlike class I MHC, class II molecules are only expressed on "antigen presenting cells" such as B-lymphocytes, macrophages, dendritic cells, endothelial cells, and a few others. T-epitopes become associated with class II MHC when an antigen comprising the T epitope binds to the surface of an antigen presenting cell. The antigen enters the cell via phagocytosis or by receptor mediated endocytosis in clathrin coated vesicles. Alternatively, soluble antigens may be internalized by fluid phase pinocytosis. Once the antigen is internalized it is processed by cellular proteases in acidic vesicles resulting in peptides 10-20 amino acids long. These epitopes bind MHC class II molecules in intracellular vesicles and the complex is transported to the cell surface. The presence of the MHC class II-antigen complex on the surface of antigen presenting cells results in the stimulation of subpopulations of T helper cells. These cells aid CTL function as well as B cell responses. In addition, T helper cells can mediate inflammatory responses.

Brief Summary Text (13):
Two important factors in determining the character of an immune response are the nature of the antigen that is recognized and the intracellular or extracellular targeting of the antigen. Thus, a T cell epitope that can be targeted to enter an antigen presenting cell in a receptor mediated endocytosis dependent way will become associated with class II MHC and activate T helper cells but not CTL cells. Moreover, if a foreign T cell epitope can be directed to the cytoplasm of a target cell in a receptor mediated endocytosis independent fashion, the epitope will become associated with class I MHC and permit the activation of CTL cells. Therefore, there exists a need in the art to specifically target epitopes in order to selectively activate a cell

mediated or humoral immune response.

Brief Summary Text (18):
In a specific embodiment of this invention the permissive site of the Bordetella pertussis adenylate cyclase is selected from the group consisting of residues 137-138, residues 224-225, residues 228-229, residues 235-236 and residues 317-318. In other specific embodiments of this invention the heterologous epitope of the recombinant Bordetella pertussis adenylate cyclase is epitope 18-132 of the nucleoprotein of the lymphocytic choriomeningitis virus, an epitope of HIV virus, in particular the epitope included in the V3 loop, an epitope of influenza virus, or an epitope of poliovirus, in particular epitope 103-116 of poliovirus.

Detailed Description Text (11):
The adenylate cyclase of Bordetella pertussis represents a suitable vehicle to specify the immunogenic response of a heterologous peptide epitope in embodiments of this invention. The Bordetella pertussis adenylate cyclase constitutes one of the essential toxins of this organism which is the causative agent of whooping cough. The adenylate cyclase is secreted by Bordetella pertussis and possesses the ability to enter target eukaryotic cells where, activated by calmodulin (CAM), it catalyzes the synthesis of cyclic AMP (cAMP) thereby impairing cellular metabolism. The adenylate cyclase (AC) is synthesized and secreted in the form of a polypeptide of 1706 amino acids: the calmodulin-dependent catalytic activity is localized in the first 400 amino acids. The C-terminal portion of approximately 1300 residues is responsible for the binding to the target cells and for the translocation of the N-terminal catalytic domain through the cytoplasmic membrane of these cells. In addition, this C-terminal portion possesses a weak hemolytic activity.

Detailed Description Text (14):
2) the adenylate cyclase may be internalized by the target cells independent of a receptor mediated endocytosis process suggesting that the catalytic domain of the toxin is capable of penetrating directly through the cytoplasmic membrane of the target cells;

Detailed Description Text (43):
The molecules of recombinant toxin may also be used to present epitopes recognized by CD4.sup.+ T lymphocytes. These epitopes will be inserted either alone or in combination with other T or B epitopes. There may thus be inserted the T epitopes 103-116 of the poliovirus, alone or in continuity with the B epitope 93-103, T epitopes of the HIV virus, and in particular the T epitope included in the V3 loop, or the T epitope of the lymphocytic choriomeningitis virus included in the region 118-132 of the nucleoprotein. The sequence of region 118-132 of the nucleoprotein of lymphocytic choriomeningitis virus is RPQASGVYMGNLTAQ (SEQ ID NO:3:)

Detailed Description Text (46):
For the generation of helper CD4.sup.+ T responses, the T epitopes will preferably be inserted into the C-terminal region of the toxin capable of entering the presenter cell by an endocytosis pathway. Toxin molecules possessing AC activity or mutated to lose this activity may be used, depending on the type of CD4.sup.+ response desired. The recombinant molecule can consist of a fragment or the complete adenylate cyclase protein expressing foreign epitope(s).

Detailed Description Text (62):
The potential importance of B. pertussis AC toxin compared to other immunotoxins lies in the fact that the poisoning of the target cells by the AC is independent of a receptor mediated endocytosis process. Thus, any surface marker specific to a given cell could serve as a receptor for targeting the recombinant AC toxin comprising a truncated AC toxin fused with a specific ligand.

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L13: Entry 2 of 16 File: USPT Oct 13, 1998

US-PAT-NO: 5821238
DOCUMENT-IDENTIFIER: US 5821238 A

TITLE: Recombinant pseudomonas exotoxin with increased activity

DATE-ISSUED: October 13, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Pastan; Ira H.	Potomac	MD		
Fitzgerald; David J.	Silver Springs	MD		

US-CL-CURRENT: 424/134.1; 424/179.1, 424/183.1, 424/832, 435/69.7, 514/12, 530/350, 530/387.1, 530/387.3, 530/387.7, 530/391.7, 530/825

CLAIMS:

What is claimed is:

1. A method for impairing tumor growth in a patient comprising administering to the patient intravenously, into a body cavity or into a lumen of an organ a ligand binding agent specific for a tumor cell, fused to a recombinant Pseudomonas exotoxin molecule in which:

(a) domain Ia is deleted;

(b) from 1 to 28 amino acids from the amino terminal end of domain II are deleted;

(c) a methionine occurs at the resultant amino terminal of said molecule; and,

(d) said molecule has increased toxic activity to a target cell as compared to an unmodified PE40.

2. The method of claim 1, wherein the recombinant Pseudomonas exotoxin molecule has amino acids 280 to 364 and 381 to 613 of Sequence ID No: 1 wherein residue 364 is peptide bonded to residue 381.

3. The method of claim 1, wherein the Pseudomonas exotoxin molecule includes a substitution of serine for the amino acid cysteine at position 287 of Sequence ID No: 1.

4. The method of claim 1, wherein the molecule further includes an amino acid sequence at a carboxyl terminal end of the molecule selected from the group

consisting of REDLK, REDL, and KDEL.

5. The method of claim 1, wherein amino acids 604-613 of domain III in Sequence ID No: 1 are retained in the Pseudomonas exotoxin molecule.

6. A method for impairing tumor growth in a patient comprising administering to the patient intravenously, into a body cavity or into a lumen of an organ a ligand binding agent specific for a tumor cell, fused to a recombinant Pseudomonas exotoxin molecule (PE) having a deletion in the amino terminal end of domain II such that the molecule is at least 20 times more cytotoxic to target cells than unmodified PE40 in a cytotoxicity assay wherein the cytotoxicity to the target cells of unmodified PE40 and the recombinant PE molecule is measured by assaying against the target cells (i) unmodified PE40 fused to a ligand binding agent specific for the target cells and (ii) the recombinant PE molecule fused to a ligand binding agent specific for the target cells.

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L13: Entry 4 of 16 File: USPT Jan 6, 1998

US-PAT-NO: 5705156
DOCUMENT-IDENTIFIER: US 5705156 A

TITLE: Psuedomonas exotoxins of low animal toxicity and high cytocidal activity

DATE-ISSUED: January 6, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Pastan; Ira	Potomac	MD		
Fitzgerald; David	Silver Spring	MD		
Chaudhary; Vijay K.	Rockville	MD		

US-CL-CURRENT: 424/183.1; 424/192.1, 424/236.1, 424/260.1, 530/391.7

CLAIMS:

What is claimed is:

1. A method of killing cells, said method comprising contacting said cells with a cytocidal amount of a modified Pseudomonas exotoxin (PE) attached to a targeting agent that binds to a specific site on said cells, said modified PE having at least one positively charged amino acid in domain 1a substituted by an amino acid without a positive charge so the modified PE has a lower animal toxicity compared to a PE lacking the substitution, said modified PE being selected from the group consisting of a PE in which each of the amino acids numbered 57, 246, 247 and 249 is glutamic acid (PE-Glu-57, 246, 247, 249), a PE in which amino acid 57 is a glutamic acid and amino acids 241-250 are deleted (PE-Glu-57.DELTA.241-250), and a PE in which amino acid 57 is a glutamic acid and each of the amino acids numbered 246, 247, and 249 is glycine (PE-Glu-57-Gly 246, 247, 249).

2. The method of claim 1, wherein at least three positively charged amino acids are substituted.

3. The method of claim 1, wherein said modified PE has a positively charged amino acid at position 57 or between positions 246 and 249 in domain 1a substituted by an amino acid without a positive charge.

4. The method of claim 2, wherein the amino acid without a positive charge is glutamic acid or glycine.

5. The method of claim 1, wherein said targeting agent is an antibody or an antigen binding fragment thereof.

6. The method of claim 1, wherein said targeting agent is a peptide hormone.

7. The method of claim 1, wherein said targeting agent is a growth factor.

8. The method of claim 1, wherein said targeting agent is a cytokine.

9. The method of claim 1, wherein said targeting agent is an antigen.

10. The method of claim 1, wherein said targeting agent is a receptor.

11. The method of claim 1, wherein said targeting agent is IL6.

12. The method of claim 1, wherein said targeting agent is TGF.alpha..

13. The method of claim 1, wherein said targeting agent is CD4.

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L13: Entry 5 of 16 File: USPT Dec 9, 1997

US-PAT-NO: 5696237
DOCUMENT-IDENTIFIER: US 5696237 A
**** See image for Certificate of Correction ****

TITLE: Recombinant antibody-toxin fusion protein

DATE-ISSUED: December 9, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
FitzGerald; David	Silver Spring	MD		
Chaudhary; Vijay Kumar	Rockville	MD		
Pastan; Ira Harry	Potomac	MD		
Waldmann; Thomas Alexander	Silver Spring	MD		
Queen; Cary L.	Palo Alto	CA		

US-CL-CURRENT: 530/387.3; 530/388.22, 530/391.7

CLAIMS:

What is claimed is:

1. An antibody-PE40 recombinant fusion protein wherein said antibody is a single-chain Fv fragment (scFv) and said PE40 is a Pseudomonas exotoxin (PE) fragment omitting amino acids 1 through 252 possessing at least the translocating and ADP ribosylating activity of PE.

2. The fusion protein of claim 1, wherein said fusion protein has a single polypeptide chain.

3. The fusion protein of claim 2 wherein the antibody is anti-Tac(Fv).

4. A composition comprising an effective amount of the fusion protein of claim 1 to kill cells bearing a receptor or an antigen to which the antibody binds, and a pharmaceutically acceptable carrier.

5. The composition of claim 4, wherein the antibody is anti-Tac(Fv).

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L13: Entry 6 of 16 File: USPT Mar 4, 1997

US-PAT-NO: 5608039
DOCUMENT-IDENTIFIER: US 5608039 A

TITLE: Single chain B3 antibody fusion proteins and their uses

DATE-ISSUED: March 4, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Pastan; Ira	Potomac	MD		
Willingham; Mark	Summerville	SC		
Fitzgerald; David	Rockville	MD		
Brinkmann; Ulrich	Kensington	MD		
Pai; Lee	Silver Spring	MD		

US-CL-CURRENT: 530/387.3; 435/69.1, 435/69.7, 435/91.1, 530/387.1, 530/387.5, 530/387.7, 530/388.1, 530/388.8, 530/390.5 , 530/866, 530/867, 536/23.53

CLAIMS:

What is claimed is:

1. A recombinant DNA molecule that encodes a single chain fusion protein, said recombinant DNA molecule comprising:

a) a DNA sequence that encodes the Fv region of both the light and the heavy chains of an antibody; and

b) a DNA sequence that encodes an effector molecule selected from the group consisting of a truncated Pseudomonas exotoxin, and a detectable label, wherein said fusion protein specifically binds an epitope bound by monoclonal antibody B3 (ATCC Accession Number HB10569).

2. The recombinant DNA molecule of claim 1, wherein said effector molecule is a Pseudomonas exotoxin.

3. The recombinant DNA molecule of claim 2, wherein said effector molecule is selected from the group consisting of PE38, PE40, PE38KDEL, and PE38REDL.

4. The recombinant DNA molecule of claim 1, wherein said antibody is B3.

5. The recombinant DNA molecule of claim 1, wherein said molecule encodes a

fusion protein selected from the group consisting of B3(Fv)-PE38, B3(Fv)-PE40, B3(Fv)-PE38KDEL, and B3(Fv)-PE38REDL.

6. A recombinantly produced single chain fusion protein comprising:

a) the Fv region of both the light and heavy chains of an antibody; and b) an effector molecule; wherein said Fv region and said effector molecule are recombinantly fused to form a single chain molecule that has the binding specificity of monoclonal antibody B3.

7. The fusion protein of claim 6, wherein said effector molecule is a Pseudomonas exotoxin.

8. The fusion protein of claim 7, wherein said effector molecule is selected from the group consisting of PE38, PE40, PE38KDEL and PE38REDL.

9. The fusion protein of claim 6, wherein said antibody is B3.

10. The fusion protein of claim 6, wherein said fusion protein is selected from the group consisting of B3(Fv)-PE38, B3(Fv)-PE40, B3(Fv)-PE38KDEL, and B3(Fv)-PE38REDL.

11. A recombinant DNA molecule that encodes a single chain antibody, said recombinant DNA molecule comprising a DNA sequence that encodes the Fv region of both the light and heavy chains of an antibody; wherein said DNA sequences are recombinantly fused to form a single molecule and wherein said fusion protein has the binding specificity of monoclonal antibody B3.

12. The recombinant DNA molecule of claim 11, wherein said antibody is B3.

13. A recombinantly produced single chain antibody comprising an Fv region of both a light and a heavy chain of an antibody where said light and heavy chains are recombinantly fused to form a single molecule which has the binding specificity of monoclonal antibody B3.

14. The single chain antibody of claim 13, wherein said antibody is B3.

15. A pharmaceutical composition comprising a recombinantly produced single chain fusion protein in a concentration sufficient to inhibit tumor cell growth, together with a pharmaceutically acceptable carrier wherein said fusion protein comprises:

a) a single-chain Fv region of an antibody, said Fv region comprising the V.sub.H and V.sub.L regions of said antibody; and

b) an effector molecule; wherein said Fv region and said effector molecule are recombinantly fused to form a single molecule that has the binding specificity of monoclonal antibody B3.

16. The composition of claim 15, wherein said effector molecule is a Pseudomonas exotoxin.

17. The composition of claim 16, wherein said effector molecule is selected from the group consisting of PE38, PE40, PE38KDEL, and PE38REDL.

18. The composition of claim 17 wherein said antibody is B3.

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L13: Entry 7 of 16 File: USPT Feb 11, 1997

US-PAT-NO: 5602095
DOCUMENT-IDENTIFIER: US 5602095 A

TITLE: Recombinant pseudomonas exotoxin with increased activity

DATE-ISSUED: February 11, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Pastan; Ira H.	Potomac	MD		
Fitzgerald; David J.	Silver Springs	MD		

US-CL-CURRENT: 514/12; 424/192.1, 424/193.1, 424/236.1, 435/252.3, 435/252.33, 435/320.1, 435/69.1, 435/69.3, 435/69.7, 514/2, 530/350, 530/351, 530/403, 530/825, 930/200

CLAIMS:

What is claimed is:

1. An isolated and purified recombinant Pseudomonas exotoxin (PE) molecule having a deletion in the amino terminal end of domain II such that the molecule is at least twenty times more cytotoxic to target cells than unmodified PE40 in a cytotoxicity assay wherein the cytotoxicity to the target cells of unmodified PE40 and the recombinant PE molecule is measured by assaying against the target cells (i) PE40 fused to a ligand binding agent specific for the target cells and (ii) the recombinant PE molecule fused to a ligand binding agent specific-for the target cells.

2. The recombinant PE of claim 1, wherein the molecule has amino acids 280 to 364 and 381 to 613 of Sequence ID NO: 1 wherein residue 364 is peptide bonded to residue 381.

3. The recombinant PE of claim 1, wherein the molecule includes a substitution of serine for the amino acid cysteine at position 287 of Sequence ID No: 1.

4. The recombinant PE of claim 1, wherein the molecule further includes an amino acid sequence at a carboxyl terminal end of the molecule selected from the group consisting of REDLK, REDL, and KDEL.

5. The recombinant PE of claim 1, wherein the molecule further comprises a deletion in domain III.

6. The recombinant PE of claim 5, wherein amino acids 604-613 of domain III in Sequence ID No: 1 are retained.

7. An isolated and purified recombinant Pseudomonas exotoxin (PE), molecule in which:

(a) domain la is deleted;

(b) from 1 to 28 amino acids from the amino terminal end of domain II are deleted;

(c) a methionine at the resultant amino terminal of said molecule; and,

(d) said molecule has increased toxic activity to a target cell as compared to an unmodified PF40.

8. The recombinant PE of claim 7, wherein the molecule has amino acids 280 to 364 and 381 to 613 of Sequence ID NO: 1 wherein residue 364 is peptide bonded to residue 381.

9. The recombinant PE of claim 7, wherein the molecule includes a substitution of serine for the amino acid cysteine at position 287 of Sequence ID No: 1.

10. The recombinant PE of claim 7, wherein the molecule further includes an amino acid sequence at a carboxyl terminal end of the molecule selected from the group consisting of REDLK, REDL, and KDEL.

11. The recombinant PE of claim 7, wherein the molecule further comprises a deletion in domain III.

12. The recombinant PE of claim 11, wherein amino acids 604-613 of domain III in Sequence ID No: 1 are retained.

13. A pharmaceutical composition comprising the molecule of claim 7 and a pharmaceutically acceptable carrier.

L13: Entry 8 of 16 File: USPT Dec 24, 1996

US-PAT-NO: 5587455
DOCUMENT-IDENTIFIER: US 5587455 A

TITLE: Cytotoxic agent against specific virus infection

DATE-ISSUED: December 24, 1996

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Berger; Edward A.	Rockville	MD		
Moss; Bernard	Bethesda	MD		
Fuerst; Thomas R.	Gaithersburg	MD		
Pastan; Ira	Potomac	MD		
Fitzgerald; David	Rockville	MD		
Mizukami; Tamio	Machida			JP
Chaudhary; Vijay K.	New Delhi			IN

US-CL-CURRENT: 530/324; 530/350

CLAIMS:

What is claimed is:

1. A hybrid protein comprising a virus binding region from a cellular receptor sequence linked to a protein toxin sequence containing a region essential for cell toxicity, wherein said cellular receptor sequence is CD4.

2. The hybrid protein of claim 1 wherein the cellular receptor sequence is from CD4 and protein toxin sequence is from Pseudomonas exotoxin A.

3. A composition comprising the hybrid protein of claim 1 in an amount sufficient to kill a HIV-infected cell.

4. A hybrid protein according to claim 1 wherein the hybrid protein comprises a sequence of human CD4 containing a binding site for HIV linked to a cytotoxic protein, and wherein said hybrid protein binds to an HIV infected cell through said binding site, is internalized into and kills the HIV infected cell.

5. The hybrid protein of claim 2 wherein said protein is a recombinant fusion protein consisting of the first 178 amino acids of the CD4 cellular receptor and amino acids 1 to 3 and 253 to 613 of the Pseudomonas exotoxin A.

6. The composition of claim 3 further comprising a pharmaceutically acceptable, sterile, non-toxic carrier.

7. The hybrid protein according to claim 4 wherein the cytotoxic protein comprises a translocation and ADP-ribosylation domain.

8. The hybrid protein according to claim 4 wherein the cytotoxic protein is selected from the group consisting of Pseudomonas exotoxin A, diphtheria toxin fragment and ricin A.

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L13: Entry 9 of 16 File: USPT Apr 30, 1996

US-PAT-NO: 5512658
DOCUMENT-IDENTIFIER: US 5512658 A

TITLE: Pseudomonas exotoxins (PE) and conjugates thereof having lower animal toxicity with high cytocidal activity through substitution of positively charged amino acids

DATE-ISSUED: April 30, 1996

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Pastan; Ira	Potomac	MD		
Fitzgerald; David	Silver Spring	MD		
Chaudhary; Vijay K.	Rockville	MD		

US-CL-CURRENT: 530/350; 424/183.1, 424/236.1, 424/260.1, 435/69.1, 435/69.7, 435/71.3, 435/875, 530/387.3, 530/391.7

CLAIMS:

What is claimed is:

1. A recombinant mutant Pseudomonas exotoxin (PE) having a positively charged amino acid residue in domain 1a substituted by an amino acid residue without a positive charge, so that the mutant PE has a lower animal toxicity compared to the unsubstituted molecule, said mutant PE being selected from the group consisting of a PE in which amino acids 57, 246, 247 and 249 are glutamic acid (PE-Glu-57,246,247,249), a PE in which amino acid 57 is a glutamic acid and amino acids 241-250 are deleted (PE-Glu-57.DELTA.241-250) and a PE in which amino acid 57 is a glutamic acid and amino acids 246, 247, and 249 are glycine (PE-Glu-57-Gly246,247,249).

2. A recombinant mutant Pseudomonas exotoxin (PE) attached to a targeting agent which recognizes a specific site on a cell targeted to be killed selected from the group consisting of IL6 attached to a PE in which amino acids 57, 246, 247 and 249 are glutamic acid (IL6-PE66-4-Glu), an IL6 attached to a PE in which amino acid 57 is glutamic acid and amino acids 246, 247 and 249 are glycine (IL6-PE-Glu-57Gly246,247,249), a TGF.alpha. attached to a PE in which amino acids 57, 246, 247 and 249 are glutamic acid (TGF.alpha.-PE66-4Glu) and CD4 attached to a PE in which amino acid 57 is glutamic acid and amino acids 246, 247 and 249 are glycine (CD4-PE66-4Glu).

3. The PE of claim 2 being IL6-PE66-4Glu.

4. The PE of claim 2 being IL6-PEGlu57Gly246,247,249.

5. The PE of claim 2 being TGFa-PE66-4Glu.

6. The PE of claim 2 being CD4-PE66-4Glu.

7. A composition comprising a cytocidal amount of the PE of claim 2 and a pharmaceutically acceptable carrier.

8. A recombinant mutant Pseudomonas exotoxin (PE) comprising IL6-domainII-PE40.

9. A composition comprising a cytocidal amount of the recombinant mutant Pseudomonas exotoxin (PE) of claim 8 to kill cells bearing IL6 receptors, and a pharmaceutically acceptable carrier.

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L13: Entry 10 of 16 File: USPT Oct 17, 1995

US-PAT-NO: 5458878
DOCUMENT-IDENTIFIER: US 5458878 A

TITLE: P. exotoxin fusio proteins have COOHG220101al alterations which increase cytotoxicity

DATE-ISSUED: October 17, 1995

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Pastan; Ira	Potomac	MD		
Chaudhary; Vijay K.	Rockville	MD		
Fitzgerald; David	Silver Spring	MD		

US-CL-CURRENT: 424/260.1; 424/279.1, 435/69.7, 530/387.3, 530/391.7

CLAIMS:

What is claimed is:

1. A fusion protein comprising a recombinant Pseudomonas exotoxin (PE) molecule, a first recognition moiety for binding a target cell, and a carboxyl terminal sequence of 4 to 16 residues which permits translocation of said fusion protein into the target cell cytosol, the first recognition moiety being inserted in domain III of PE after residue 600 and before residue 613.

2. The fusion protein of claim 1, wherein the carboxyl terminal sequence comprises, in a direction from the amino terminus to the carboxyl terminus, the following amino acid residues:

R.sup.1 --R.sup.2 --R.sup.3 --R.sup.4 --(R.sup.5).sub.n

wherein,

R.sup.1 is a positively charged amino acid residue;

R.sup.2 is a negatively charged amino acid residue;

R.sup.3 is a negatively charged amino acid residue;

R.sup.4 is L; and

R.sup.5 is a positively charged amino acid residue;

and wherein n is zero or 1.

3. The fusion protein of claim 2, wherein R.sup.1 is selected from the group consisting of R and K.

4. The fusion protein of claim 2, wherein R.sup.2 is selected from the group consisting of E and D.

5. The fusion protein of claim 2, wherein R.sup.3 is selected from the group consisting of D and E.

6. The fusion protein of claim 2, wherein n is 1 and R.sup.5 is selected from the group consisting of K and R.

7. The fusion protein of claim 2, wherein the carboxyl terminal sequence is selected from the group consisting of REDLK, KEDLK, REDLR, REDL, and KDEL.

8. The fusion protein of claim 2, wherein the carboxyl terminal sequence is KDELKDELKDEL.

9. The fusion protein of claim 2, wherein the first recognition molecule is an antibody or a portion of an antibody which recognizes the target cell.

10. The fusion protein of claim 2, wherein the first recognition molecule is selected from the group consisting of a growth factor, lymphokine, cytokine, and a hormone.

11. The fusion protein of claim 2, wherein the first recognition molecule is TGF.alpha. or CD4.

12. The fusion protein of claim 2, wherein the first recognition molecule is inserted after residue 607 of the PE molecule.

13. The fusion protein of claim 2, wherein a second recognition molecule is inserted in the toxin molecule.

14. The fusion protein of claim 13, wherein the second recognition molecule is different from the first recognition molecule.

15. The fusion protein of claim 13, wherein the second recognition molecule is anti-Tac (Fv).

16. The fusion protein of claim 13, wherein the recombinant PE molecule is TGF.alpha.-anti-Tac(Fv)-PE40.

17. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a fusion protein comprising a recombinant Pseudomonas exotoxin (PE) molecule, a first recognition moiety for binding a target cell, and a carboxyl terminal sequence of 4 to 16 residues which permits translocation of said fusion protein into the target cell cytosol, the first recognition moiety being inserted in domain III of PE after residue 600 and before residue 613.

18. The composition of claim 17, wherein the carboxyl terminal sequence comprises, in a direction from the amino terminus to the carboxyl terminus, the following amino acid residues:

R.sup.1 --R.sup.2 --R.sup.3 --R.sup.4 --(R.sup.5).sub.n

wherein,

R.sup.1 is a positively charged amino acid residue;

R.sup.2 is a negatively charged amino acid residue;

R.sup.3 is a negatively charged amino acid residue;

R.sup.4 is L; and

R.sup.5 is a positively charged amino acid residue;

and wherein n is zero or 1.

19. The composition of claim 17, wherein the carboxyl terminal residues are selected from the group consisting of REDLK, KEDLK, REDLR, REDL, and KDEL.

20. The fusion protein of claim 7 wherein the carboxyl terminal sequence is REDLK.

21. The fusion protein of claim 7 wherein the carboxyl terminal sequence is KEDLK.

22. The fusion protein of claim 7 wherein the carboxyl terminal sequence is REDLR.

23. The fusion protein of claim 7 wherein the carboxyl terminal sequence is REDL.

24. The fusion protein of claim 7 wherein the carboxyl terminal sequence is KDEL.

25. The fusion protein of claim 19 wherein the carboxyl terminal sequence is REDLK.

26. The composition of claim 19 wherein the carboxyl terminal sequence is KEDLK.

27. The composition of claim 19 wherein the carboxyl terminal sequence is REDLR.

28. The composition of claim 19 wherein the carboxyl terminal sequence is REDL.

29. The fusion protein of claim 19 wherein the carboxyl terminal sequence is KDEL.

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L13: Entry 10 of 16 File: USPT Oct 17, 1995

US-PAT-NO: 5458878
DOCUMENT-IDENTIFIER: US 5458878 A

TITLE: P. exotoxin fusio proteins have COOHG220101al alterations which increase cytotoxicity

DATE-ISSUED: October 17, 1995

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Pastan; Ira	Potomac	MD		
Chaudhary; Vijay K.	Rockville	MD		
Fitzgerald; David	Silver Spring	MD		

US-CL-CURRENT: 424/260.1; 424/279.1, 435/69.7, 530/387.3, 530/391.7

CLAIMS:

What is claimed is:

1. A fusion protein comprising a recombinant Pseudomonas exotoxin (PE) molecule, a first recognition moiety for binding a target cell, and a carboxyl terminal sequence of 4 to 16 residues which permits translocation of said fusion protein into the target cell cytosol, the first recognition moiety being inserted in domain III of PE after residue 600 and before residue 613.

2. The fusion protein of claim 1, wherein the carboxyl terminal sequence comprises, in a direction from the amino terminus to the carboxyl terminus, the following amino acid residues:

R.sup.1 --R.sup.2 --R.sup.3 --R.sup.4 --(R.sup.5).sub.n

wherein,

R.sup.1 is a positively charged amino acid residue;

R.sup.2 is a negatively charged amino acid residue;

R.sup.3 is a negatively charged amino acid residue;

R.sup.4 is L; and

R.sup.5 is a positively charged amino acid residue;

and wherein n is zero or 1.

3. The fusion protein of claim 2, wherein R.sup.1 is selected from the group consisting of R and K.

4. The fusion protein of claim 2, wherein R.sup.2 is selected from the group consisting of E and D.

5. The fusion protein of claim 2, wherein R.sup.3 is selected from the group consisting of D and E.

6. The fusion protein of claim 2, wherein n is 1 and R.sup.5 is selected from the group consisting of K and R.

7. The fusion protein of claim 2, wherein the carboxyl terminal sequence is selected from the group consisting of REDLK, KEDLK, REDLR, REDL, and KDEL.

8. The fusion protein of claim 2, wherein the carboxyl terminal sequence is KDELKDELKDEL.

9. The fusion protein of claim 2, wherein the first recognition molecule is an antibody or a portion of an antibody which recognizes the target cell.

10. The fusion protein of claim 2, wherein the first recognition molecule is selected from the group consisting of a growth factor, lymphokine, cytokine, and a hormone.

11. The fusion protein of claim 2, wherein the first recognition molecule is TGF.alpha. or CD4.

12. The fusion protein of claim 2, wherein the first recognition molecule is inserted after residue 607 of the PE molecule.

13. The fusion protein of claim 2, wherein a second recognition molecule is inserted in the toxin molecule.

14. The fusion protein of claim 13, wherein the second recognition molecule is different from the first recognition molecule.

15. The fusion protein of claim 13, wherein the second recognition molecule is anti-Tac (Fv).

16. The fusion protein of claim 13, wherein the recombinant PE molecule is TGF.alpha.-anti-Tac(Fv)-PE40.

17. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a fusion protein comprising a recombinant Pseudomonas exotoxin (PE) molecule, a first recognition moiety for binding a target cell, and a carboxyl terminal sequence of 4 to 16 residues which permits translocation of said fusion protein into the target cell cytosol, the first recognition moiety being inserted in domain III of PE after residue 600 and before residue 613.

18. The composition of claim 17, wherein the carboxyl terminal sequence comprises, in a direction from the amino terminus to the carboxyl terminus, the following amino acid residues:

R.sup.1 --R.sup.2 --R.sup.3 --R.sup.4 --(R.sup.5).sub.n

wherein,

R.sup.1 is a positively charged amino acid residue;

R.sup.2 is a negatively charged amino acid residue;

R.sup.3 is a negatively charged amino acid residue;

R.sup.4 is L; and

R.sup.5 is a positively charged amino acid residue;

and wherein n is zero or 1.

19. The composition of claim 17, wherein the carboxyl terminal residues are selected from the group consisting of REDLK, KEDLK, REDLR, REDL, and KDEL.

20. The fusion protein of claim 7 wherein the carboxyl terminal sequence is REDLK.

21. The fusion protein of claim 7 wherein the carboxyl terminal sequence is KEDLK.

22. The fusion protein of claim 7 wherein the carboxyl terminal sequence is REDLR.

23. The fusion protein of claim 7 wherein the carboxyl terminal sequence is REDL.

24. The fusion protein of claim 7 wherein the carboxyl terminal sequence is KDEL.

25. The fusion protein of claim 19 wherein the carboxyl terminal sequence is REDLK.

26. The composition of claim 19 wherein the carboxyl terminal sequence is KEDLK.

27. The composition of claim 19 wherein the carboxyl terminal sequence is REDLR.

28. The composition of claim 19 wherein the carboxyl terminal sequence is REDL.

29. The fusion protein of claim 19 wherein the carboxyl terminal sequence is KDEL.

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L13: Entry 11 of 16 File: USPT Jul 12, 1994

US-PAT-NO: 5328984
DOCUMENT-IDENTIFIER: US 5328984 A
**** See image for Certificate of Correction ****

TITLE: Recombinant chimeric proteins deliverable across cellular membranes into cytosol of target cells

DATE-ISSUED: July 12, 1994

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Pastan; Ira H.	Potomac	MD		
Trevor; Prior	Bethesda	MD		
Fitzgerald; David J.	Silver Spring	MD		
Debinski; Waldemar	Gaithersburg	MD		
Siegall; Clay	Silver Springs	MD		

US-CL-CURRENT: 424/134.1; 435/69.7, 530/350, 530/387.3, 530/399, 530/402, 536/23.4

CLAIMS:

What is claimed is:

1. A chimeric protein of which a portion is translocated across a cellular membrane into the cytosol of target cells, the chimeric protein comprising, linked together at least (1) a first segment comprising a foreign protein desired to be introduced into the cytosol of the target cells, (2) a second segment from Domain II of Pseudomonas exotoxin having a translocation function which delivers the foreign protein across the cellular membrane into the cytosol of the target cells, and (3) a third segment which binds the chimeric protein to the target cells, the foreign protein being otherwise impermeable to the target cells and heterologous to the second segment.

2. The chimeric protein of claim 1, wherein said third segment is a ligand, an antibody, a growth factor or a cytokine for selective recognition of target cells.

3. The chimeric protein of claim 1, being PE-Bar.

4. The chimeric protein of claim 1, being PE.sup..DELTA..sbsp.553 -Bar.

5. A DNA molecule having a sequence that encodes the chimeric protein of claim 1.

6. A method for introducing a foreign protein across a cellular membrane into the cytosol of target cells, comprising the step of contacting cells into which a foreign protein is desired to be introduced, with the chimeric protein of claim 1.

7. A composition comprising an effective amount of the chimeric protein of claim 1 and pharmaceutically acceptable carrier.

8. A chimeric protein comprising:

a first segment comprising a foreign protein;

a second segment from Domain II of Pseudomonas exotoxin which translocates the first segment across a cellular membrane; and

a third segment which binds the chimeric protein to a target cell;

wherein the foreign protein is heterologous to the second segment.

9. The chimeric protein of claim 8, wherein the third segment is a ligand, an antibody, a growth factor or a cytokine.

10. The chimeric protein of claim 8, wherein the third segment is Domain Ia of Pseudomonas exotoxin.

11. The chimeric protein of claim 8, wherein the foreign protein is selected from the group consisting of barnase and somatostatin.

12. A DNA molecule sequence that encodes a chimeric protein having a foreign protein segment, a segment from Domain II of Pseudomonas exotoxin that has a translocation function which delivers the foreign protein across cellular membranes into the cytosol of target cells all linked to a third segment which encodes a protein that binds the chimeric protein to the target cells, the foreign protein being otherwise impermeable to the target cells and heterologous to the protein having the translocation function.

13. A method of making a translocatable chimeric protein, comprising the step of making a chimeric gene by linking together at least (1) a foreign protein gene sequence that encodes a foreign protein desired to be introduced into the cytosol of a target cell, (2) a heterologous gene sequence from a sequence encoding Domain II of Pseudomonas exotoxin that encodes a protein having a translocation function which delivers the foreign protein across the cellular membrane into the cytosol of the target cell, and (3) a gene sequence encoding a protein which binds the chimeric protein to the target cell, then allowing the expression of said chimeric gene in a suitable expression system so that a translocatable chimeric protein is obtained, and then recovering said chimeric protein from said expression system.

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L13: Entry 12 of 16 File: USPT Jan 21, 1992

US-PAT-NO: 5082927
DOCUMENT-IDENTIFIER: US 5082927 A

TITLE: Selectively cytotoxic IL-4-PE40 fusion protein

DATE-ISSUED: January 21, 1992

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Pastan; Ira	Potomac	MD		
FitzGerald; David	Silver Spring	MD		
Ogata; Masato	Rockville	MD		

US-CL-CURRENT: 530/351; 424/192.1, 424/85.1, 424/85.2, 435/4, 435/69.5, 435/69.52, 435/71.3, 514/2, 514/8, 530/402, 530/403, 530/404, 530/405, 530/406, 530/820, 530/825

CLAIMS:

What is claimed is:

1. A functionally active recombinant IL-4-PE40 fusion protein that selectively kills cells bearing IL-4 receptors, without killing cells lacking IL-4 receptors, wherein the fusion protein has ADP ribosylating properties.

2. The recombinant fusion protein of claim 1 produced by employing plasmid pM048 in an expression vector.

3. A composition, comprising an effective amount of the recombinant fusion protein of claim 1 and pharmaceutically acceptable carrier.

4. A mutant form of the fusion protein of claim 1 which consist of IL-4-PE40 Asp.sup.553.

L13: Entry 13 of 16 File: USPT Sep 18, 1990

US-PAT-NO: 4958009
DOCUMENT-IDENTIFIER: US 4958009 A

TITLE: Anti-human ovarian cancer immunotoxins and methods of use thereof

DATE-ISSUED: September 18, 1990

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Bjorn; Michael J.	Hercules	CA		
FitzGerald; David J.	Fairfax	VA		
Frankel; Arthur E.	Durham	NC		
Laird; Walter J.	Pinole	CA		
Pastan; Ira H.	Potomac	MD		
Ring; David B.	Redwood City	CA		
Willingham; Mark C.	Bethesda	MD		
Windelhake; Jeffrey L.	Alameda	CA		

US-CL-CURRENT: 424/183.1; 424/155.1, 424/156.1, 424/804, 424/807, 514/885, 530/388.8, 530/388.85, 530/391.7, 530/808, 530/864

CLAIMS:

What is claimed is:

1. Immunotoxin comprising a cytotoxic moiety and a monoclonal antibody wherein said monoclonal antibody

(i) binds human ovarian cancer tissue;

(ii) has a selectivity of about 0.11 or less;

(iii) is an IgG or IgM;

said immunotoxin having at least one capability selected from the group consisting of:

a cytotoxicity ID.sub.50 of about 10nM or less against human ovarian cancer cells; retarding the rate of growth of tumors comprised of human ovarian cancer cells carried by a mammal when said mammal is treated with said immunotoxin; or

extending the survival time of a mammal bearing a tumor comprised of human ovarian cancer cells when said mammal is treated with said immunotoxin.

2. The immunotoxin of claim 1 wherein the human ovarian cancer cells are at least one selected from the groups consisting of OVCAR-2, OVCAR-3, OVCAR-4, OVCAR-5 and A1847.

3. The immunotoxin of claim 1 wherein said monoclonal is selected from the groups consisting of 2G3, (ATCC Accession No. HB8491), 9C6, (In Vitro Accession No. IVI10065), 33F8, (ATCC Accession No. HB8697), 44B2, (In Vitro Accession No. IVI10068), 44F4, (In Vitro Accession No. IVI10058), 120H7, (In Vitro Accession No. IVI10061), 200F9, (In Vitro Accession No. IVI10062), 204F4, (In Vitro Accession No. IVI10071), 219F3, (IVI10072), 245E7, (ATCC Accession No. HB8489), 260F9, (ATCC Accession No. HB8488), 266B2, (HB8486), 280D11, (ATCC Accession No. HB8487), 317G5, (ATCC Accession No. HB8485), 369F10, (HB8682), 388D4, (In Vitro Accession No. IVI10065), 421E8, (In Vitro Accession No. IVI10064), 451C3, (In Vitro Accession No. IVI 10081), 454A12, (In Vitro Accession No. IVI 10075), 454C11, (In Vitro Accession No. IVI10075), 650E2, (In Vitro Accession No. IVI10083), 788G6, (ATCC Accession No. HB8692) and 871E3 (In Vitro Acession No. IVI10084).

4. The immunotoxin of claim 1 wherein said monoclonal antibody binds a high molecular weight mucin.

5. The immunotoxin of claim 1 wherein said monoclonal antibody binds to a 55 Kd antigen.

6. The immunotoxin of claim 5 wherein the monoclonal antibody binds an epitope which can be bound by 260F9 and 266B2.

7. The immunotoxin of claim 1 wherein said monoclonal antibody binds a 200 Kd antigen.

8. The immunotoxin of claim 1 wherein said monoclonal antibody binds a 42 Kd proteinaceous antigen.

9. The immunotoxin of claim 1 wherein the toxic moiety is an enzymatically active toxin of bacterial, plant or fungal origin.

10. The immunotoxin of claim 1 wherein the toxic moiety is selected from the group consisting of ricin toxin A chain, Phytolacca americana proteins, diphtheria toxin A fragment, non-binding active fragments of diphtheria toxin A fragment and Pseudomonas aeruginosa exotoxin A.

11. The immunotoxin of claim 1 wherein the toxic moiety is ricin toxin A chain.

12. The immunotoxin of claim 1 wherein the toxic moiety is Pseudomonas exotoxin A.

13. The immunotoxin of claim 12 wherein the ricin toxin A chain is recombinant ricin toxin A chain.

14. A method of extending the survival time of a mammal bearing tumors comprised of human ovarian tumor cells comprising administering to said mammal an amount of an immunotoxin of claim 1 effective to extend the survival time of said mammal.

15. The method of claim 14 wherein said immunotoxin is effective against at least one human ovarian tumor comprised of cells selected from the group consisting of OVCAR-2, -3, -4, -5 and A1847.

16. A method of retarding the rate of growth of tumors comprised of human ovarian cancer cells carried by a mammal comprising administering to said mammal an amount of an immunotoxin of claim 1 effective to retard the rate of growth of human ovarian tumors carried by said mammal.

17. The method of claim 16 wherein said immunotoxin is effective against at least one human ovarian tumor comprised of cells selected from the group consisting of OVCAR-2, -3, -4, -5 and A1847.

18. A method of killing human ovarian cancer cells comprising contacting said cells with a cytotoxically effective amount of an immunotoxin of claim 1.

19. The method of claim 18 wherein said immunotoxin is effective against at least one human ovarian cancer cell line selected from the group consisting of OVCAR-2, -3, -4, -5 and A1847.

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L13: Entry 14 of 16 File: USPT Jan 9, 1990

US-PAT-NO: 4892827
DOCUMENT-IDENTIFIER: US 4892827 A

TITLE: Recombinant pseudomonas exotoxins: construction of an active immunotoxin with low side effects

DATE-ISSUED: January 9, 1990

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Pastan; Ira H.	Potomac	MD		
Adhya; Sankar	Gaithersburg	MD		
Fitzgerald; David	Bethesda	MD		

US-CL-CURRENT: 435/193; 424/183.1, 424/94.5, 435/69.4, 435/69.52, 435/69.6, 435/69.7, 514/12, 514/2, 514/6, 530/350, 530/351, 530/370, 530/391.7, 530/395, 530/396

CLAIMS:

We claim:

1. A modified Pseudomonas exotoxin which comprises ADP ribosylating activity and the ability to translocate across a cell membrane; wherein the exotoxin comprises a deletion in the receptor binding domain Ia of the native toxin sufficient to render the modified toxin less toxic to human or animal cells in vitro and less toxic to the liver when administered in vivo relative to an unmodified Pseudomonas exotoxin.

2. The modified exotoxin of claim 1, being covalently bound to a cell recognition protein which binds to a receptor on the targeted cell membrane and selectively kills cells bearing said receptor.

3. A composition comprising a cytotoxic amount of the exotoxin of claim 2.

4. A method for achieving targeted cytotoxicity, comprising contacting cells targeted to be killed, with a cytotoxic amount of the composition of claim 3, said targeted cells being those having receptors to which said recognition protein binds, but the composition being without cytotoxicity to cells which comprise PE receptors and lack receptors for the cell recognition protein.

5. The modified exotoxin of claim 2 wherein said cell recognition protein is selected from the group consisting of an antibody, a peptide hormone, a growth factor and a cytokine.

6. The exotoxin of claim 5 wherein said cell recognition protein is an antibody.

7. The exotoxin of claim 5 wherein said growth factor is a-TGF.

8. The exotoxin of claim 5 wherein said cytokine is interleukin-2.

9. The exotoxin of claim 6 wherein said antibody is antitransferin receptor antibody.

10. The modified exotoxin of claim 1 produced by employing the plasmid of ATCC deposit number 67206, 67207, or 67208 under conditions permissive for expression of the toxin.

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L13: Entry 15 of 16 File: USPT Feb 21, 1989

US-PAT-NO: 4806494
DOCUMENT-IDENTIFIER: US 4806494 A

TITLE: Monoclonal antibody against ovarian cancer cells (OVB-3)

DATE-ISSUED: February 21, 1989

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Pastan; Ira	Potomac	MD		
Fitzgerald; David J.	Bethesda	MD		
Willingham; Mark	Bethesda	MD		

US-CL-CURRENT: 530/388.8; 424/179.1, 436/518, 436/519, 436/548, 514/2, 530/388.2, 530/391.7, 530/391.9

CLAIMS:

We claim:

1. Monoclonal antibody OVB-3 having all the characteristics of that antibody produced by the hydroma ell line which has been assigned ATCC Accession No. HB9147.

2. An immunotoxin conjugate for the chemotherapeutic alleviation of human ovarian cancer comprising a monoclonal antibody OVB-3 which specifically binds to ovarian cancer cells bonded to Pseudomonas exotoxin.

3. An immunotoxin conjugate comprising Pseudomonas exotoxin (PE) bound to a monoclonal antibody which specifically binds to ovarian cancer cells wherein said PE is modified by treatment with 2-iminothiolane followed by treatment with dithiobis(2-nitrobenzoic acid) and wherein said monoclonal antibody is modified by treatment with a reagent selected from the group consisting of 2-imminothiolane and m-maleimidobenzoyl N-hydroxysuccinimide ester under conditions which effect the formation of a disulfide or thioether bond between said PE and said monoclonal antibody.

4. A composition of matter comprising a monoclonal antibody of claim 1 conjugated with a Pseudomonas exotoxin.

5. A composition of matter comprising an monoclonal antibody of claim 1 in a carrier.

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L13: Entry 16 of 16 File: USPT Oct 8, 1985

US-PAT-NO: 4545985
DOCUMENT-IDENTIFIER: US 4545985 A

TITLE: Pseudomonas exotoxin conjugate immunotoxins

DATE-ISSUED: October 8, 1985

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Pastan; Ira	Potomac	MD		
Willingham; Mark C.	Bethesda	MD		
Fitzgerald; David J.	Wheaton	MD		

US-CL-CURRENT: 424/180.1; 424/179.1, 514/2, 514/6, 530/388.22, 530/388.23, 530/391.9, 530/404, 530/414, 530/806, 530/807 , 530/825, 530/826, 530/828

CLAIMS:

We claim:

1. A method for the chemotherapeutic alleviation of cancer in animals consisting essentially of injecting a chemotherapeutically alleviating amount of an immunotoxin conjugate which comprises a modified Pseudomonas exotoxin (PE) and a modified cancer cell binding protein wherein said PE is modified by treatment with methylmercaptobutyrimidate (MMB) followed by treatment with dithiobis(2-nitrobenzoic acid) and wherein said cancer cell binding protein is modified by treatment with a reagent selected from the group consisting of MMB and m-maleimidobenzoyl N hydroxy-succinimide ester under conditions which effect the formation of a disulfide or thioether bond between said PE and said cancer cell-binding protein.

2. The method of claim 1 wherein said Pseudomonas exotoxin is modified with methyl-4-mercapto-butyrimidate and dithiobis(2-nitrobenzoic acid).

3. The method of claim 1 wherein said cancer cell-binding protein is selected from one member of the group consisting of anti-TAC monoclonal antibody, anti-TFR monoclonal antibody, epidermal growth factor, and cysteine.

4. The method of claim 1 wherein said cell-binding protein is modified with one member of the group consisting of methyl-4-mercaptobutyrimidate and m-maleimidobenzoyl N hydroxy-succinimide ester.

5. The method of claim 1 wherein said chemotherapeutically alleviating dosage is 0.3-0.5 mg.

6. A process for the production of a cancer cell-specific immunotoxin comprising chemically bonding modified Pseudomonas exotoxin (PE) to a modified monoclonal antibody (Ab) wherein PE is modified by treatment with methylmercaptobutyrimidate and dithiobis(2-nitrobenzoic acid) and Ab is modified by one reagent selected from the group consisting of methylmercaptobutyrimidate and m-maleimidobenzoyl N hydroxysuccinimide ester under conditions which effect the formation of a disulfide or thioether bond between said PE and said Ab.

7. The process of claim 6 in which said Pseudomonas exotoxin is modified by treatment with mercaptobutyrimidate under conditions in which 2 moles of sulhydryl are used for every mole of toxin.

8. The process of claim 6 in which said monoclonal antibody is selected from one member of the group consisting of anti-TAC, specific for the human T-cell growth factor receptor; and anti-TFR, specific for a transferrin receptor.

9. The process of claim 6 wherein the chemotherapeutic activity of said toxic protein conjugate is enhanced by administering said toxic protein conjugate in the presence of a human adeno-virus.

10. An immunotoxin conjugate consisting essentially of Pseudomonas exotoxin (PE) bound to a cancer cell binding protein wherein PE is modified by treatment with methylmercaptobutyrimidate (MMB) followed by treatment with dithiobis(2-nitrobenzoic acid) and wherein said cancer cell binding protein is modified by treatment with a reagent selected from the group consisting of MMB and m-maleimidobenzoyl N-hydroxysuccinimide ester under conditions which effect the formation of a disulfide or thioether bond between said PE and said cancer cell-binding protein.

11. The conjugate of claim 10 wherein said cell-binding protein is modified with one member of the group consisting of methyl-4-mercaptobutyrimidate and m-maleimidobenzoyl N hydroxy-succinimide ester.

12. The immunotoxin conjugate of claim 10 wherein said Pseudomonas exotoxin is modified by treatment with methyl-mercaptobutyrimidate and followed by treatment with dithiobis(2-nitrobenzoic acid) under conditions in which 2 moles of sulfhydryl are used for every mole of toxin.

13. The immunotoxin conjugate of claim 10 wherein said cancer cell-binding protein is selected from the group consisting of anti-TAC monoclonal antibody, anti-TFR monoclonal antibody, epidermal growth factor, and cysteine.

14. An immunotoxin conjugate comprising modified Pseudomonas exotoxin (PE) and a modified monoclonal antibody (Ab) wherein PE is modified by treatment with methylmercaptobutyrimidate (MMB) followed by dithiobis(2-nitrobenzoic acid) wherein the monoclonal antibody is modified with a reagent selected from one member of the group consisting of MMB and m-maleimidobenzoyl N hydroxy-succinimide ester under conditions which effect the formation of a disulfide bond or thioether bond between PE and Ab.

15. An immunotoxin conjugate of claim 14 wherein said Pseudomonas exotoxin is modified by treatment with methylmercaptobutyrimidate followed by treatment with dithiobis(2-nitrobenzoic acid) under conditions in which 2 moles of sulfhydryl are used for every mole of toxin.

16. An immunotoxin comprising Pe-B-Ab wherein PE is Pseudomonas exotoxin, Ab is a monoclonal antibody selected from the group consisting of anti-TAC and anti-TFR, and B is a sulfhydryl group bridging agent wherein PE is treated with methyl-4-mercaptobutyrimidate (MMB) followed by treatment with dithiobis(2-nitrobenzoic acid) and Ab is treated with MMB under conditions which effect the formation of a disulfide or thioether bond between said PE and said

Ab.

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L14: Entry 4 of 36 File: USPT Oct 8, 2002

DOCUMENT-IDENTIFIER: US 6461617 B1
TITLE: Recombinant toxin fragments

CLAIMS:

1. A non-toxic polypeptide comprising first, second and third domains, wherein (a) said first domain comprises a botulinum toxin light chain and cleaves one or more vesicle or plasma-membrane associated proteins essential to exocytosis, (b) said second domain comprises the first 100 N-terminal amino acids of a botulinum toxin heavy chain and (i) translocates the polypeptide into a cell or (ii) increases the solubility of the polypeptide compared to the solubility of the first domain on its own or (iii) both translocates the polypeptide into a cell and increases the solubility of the polypeptide compared to the solubility of the first domain on its own, (c) said polypeptide is free of clostridial neurotoxin and free of clostridial neurotoxin precursor that can be converted into toxin by proteolytic action, (d) said polypeptide is a single polypeptide, (e) said third domain is a tandem repeat synthetic IgG binding domain derived from domain .beta. of Staphylococcal protein A, and (f) said polypeptide lacks a portion designated H.sub.c of a botulinum toxin heavy chain.

2. A non-toxin polypeptide comprising first, second and third domains, wherein (a) said first domain comprises a botulinum toxin light chain and cleaves one or more vesicle or plasma-membrane associated proteins essential to exocytosis, (b) said second domain comprises the first 100 N-terminal amino acids of a botulinum toxin heavy chains and (i) translocates the polypeptide into a cell of (ii) increases the solubility of the polypeptide compared to the solubility of the first domain on its own or (iii) both translocates the polypeptide into a cell and increases the solubility of the polypeptide compared to the solubility of the first domain on its own, (c) said polypeptide is free of clostridial neurotoxin and free of clostridial neurotoxin precursor that can be converted into toxin by proteolytic action, (d) said polypeptide is a single polypeptide, (e) said third domain is insulin-like growth-factor-1 (IGF-1), and (f) said polypeptide lacks a portion designated H.sub.c of a botulinum toxin heavy chain.

3. A non-toxin polypeptide comprising first and second domains, wherein (a) said first domain is a botulinum toxin type A light chain variant comprising a sequence correspond to amino acids 1-448 of SEQ ID NO:2 wherein three amino acid residues have been altered compared to that sequence, namely at residue 2 a glutamate, at residue 26 a lysine and at residue 27 a tyrosine which first domain cleaves one or more vesicle or plasma-membrane associated proteins essential to exocytosis, (b) said second domain comprises the first 100 N-terminal amino acids of a botulinum toxin heavy chains and (i) translocates the polypeptide into a cell of (ii) increases the solubility of the polypeptide compared to the solubility of the first domain on its own or (iii) both translocates the polypeptide into a cell and increases the solubility of the polypeptide compared to the solubility of the first domain on its own, (c) said polypeptide is free of clostridial neurotoxin and free of clostridial neurotoxin precursor that can be converted into toxin by proteolytic action, (d) said polypeptide is a single polypeptide, (e) one or both of (i) the toxin light chain or fragment or variant of toxin light chain and (ii) the portion of the toxin heavy chain are of botulinum toxin type A, and (f) said polypeptide lacks a portion

designated H.sub.c of a botulinum toxin heavy chain.

4. A non-toxin polypeptide comprising first and second domains, wherein (a) first domain comprises a botulinum toxin light chain and cleaves one or more vesicle or plasma-membrane associated proteins essential to exocytosis, (b) said second domain comprises the first 100 N-terminal amino acids of a botulinum toxin heavy chain and (i) translocates the polypeptide into a cell or (ii) increases the solubility of the polypeptide compared to the solubility of the first domain on its own or (iii) both translocates the polypeptide into a cell and increases the solubility of the polypeptide compared to the solubility of the first domain on its own, (c) said polypeptide is free of clostridial neurotoxin and free of clostridial neurotoxin precursor that can be converted into toxin by proteolytic action, (d) said polypeptide is a single polypeptide, and (e) said polypeptide lacks a portion designated H.sub.c of a botulinum toxin heavy chain.

5. A non-toxin polypeptide comprising first and second domains, wherein (a) said first domain comprises a botulinum toxin light chain and cleaves one or more vesicle or plasma-membrane associated proteins essential to exocytosis, (b) said second domain comprises the first 100 N-terminal amino acids of a botulinum toxin heavy chain and (i) translocates the polypeptide into a cell or (ii) increases the solubility of the polypeptide compared to the solubility of the first domain on its own or (iii) both translocates the polypeptide into a cell and increases the solubility of the polypeptide compared to the solubility of the first domain on its own, (c) said polypeptide is free of clostridial neurotoxin and free of clostridial neurotoxin precursor that can be converted into toxin by proteolytic action, (d) said polypeptide is a single polypeptide, (e) said second domain comprises a portion designated H.sub.N of the botulinum toxin heavy chain which consists of the 423 N-terminal amino acids of a botulinum toxin type A heavy chain, and (f) said polypeptide lacks a portion designated H.sub.c of a botulinum toxin heavy chain.

6. A polypeptide according to claim 5 wherein the first domain comprises a botulinum toxin type A light chain.

7. A polypeptide according to claim 5 wherein said first domain is a botulinum toxin type A light chain variant which comprises a sequence corresponding to amino acids 1-448 of SEQ ID NO:2 having at least three amino acid residues which are altered compared to that sequence, namely at residue 2 a glutamate, residue 26 a lysine and residue 27 a tyrosine, and wherein said polypeptide contains 423 N-terminal amino acids of a botulinum toxin type A heavy chain.

L2: Entry 3 of 68 File: USPT Feb 11, 2003

DOCUMENT-IDENTIFIER: US 6518397 B1
TITLE: Pharmaceuticals for modulating hormone responsiveness

Brief Summary Text (10):
Calreticulin was initially identified as the major Ca.sup.2+ -storage protein in the sarcoplasmic reticulum of skeletal muscle (Ostwald and MacLennan, 1974). Subsequent work has revealed that the protein can also be detected in the endoplasmic reticulum of non-muscle tissues (Fliegel et al., 1989a; Opas et al., 1991). Calreticulin has been considered to be a resident protein of the endoplasmic reticulum of a cell, where it is thought to behave as a calcium binding protein due to its high capacity calcium binding properties (Michalak et al., 1992). Calreticulin possesses many diverse functional domains such as high affinity, low capacity- and low affinity, high capacity-Ca.sup.2+ -binding sites, a C-terminal KDEL endoplasmic reticulum retention signal, and a nuclear localization signal (Michalak et al., 1992).

Detailed Description Text (32):
Although calreticulin contains a KDEL motif at its C-terminus and is therefore thought to be resident in the endoplasmic reticulum (McCauliffe et al., 1990; Fliegel et al., 1989; Michalak et al., 1992), it also has a nuclear targeting .:signal (McCauliffe et al., 1990; Michalak et al., 1992; Marzluff et al., 1985), raising the possibility that this protein is also present in the nucleus (Michalak et al., 1992). The presence of p60 in nuclei was demonstrated by affinity chromatography of human osteosarcoma cell (HOS) nuclear extracts on a KLGFFKR-affinity column [SEQ ID NO:7] (FIG. 1).

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L13: Entry 1 of 16 File: USPT Dec 29, 1998

US-PAT-NO: 5854044
DOCUMENT-IDENTIFIER: US 5854044 A

TITLE: Recombinant pseudomonas exotoxin with increased activity

DATE-ISSUED: December 29, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Pastan; Ira H.	Potomac	MD		
Fitzgerald; David J.	Silver Springs	MD		

US-CL-CURRENT: 435/194; 530/324, 530/350, 530/351, 530/387.3, 530/387.7, 530/399

CLAIMS:

What is claimed is:

1. An isolated and purified recombinant Pseudomonas exotoxin (PE) fusion protein wherein a ligand-binding-agent is fused to a PE molecule in which domain Ia is deleted and from 1 to 28 amino acids from the amino terminal end of domain II are deleted.

2. The recombinant PE of claim 1, wherein the ligand binding agent is fused after about amino acid position 607 and is followed by amino acids 604-613 of domain III.

3. The recombinant PE of claim 1, wherein the ligand binding agent is TGF.alpha..

4. The recombinant PE of claim 1, wherein the ligand binding agent is an antibody or binding fragment thereof.

5. The recombinant PE of claim 1, wherein the ligand binding agent is a hormone.

6. The recombinant PE of claim 1, wherein the ligand binding agent is a growth factor.

7. The recombinant PE of claim 1, wherein the ligand binding agent specifically binds a cancer cell receptor.

8. The recombinant PE of claim 1, comprising amino acids 280 to 364 and 381 to 613 of PE with TGF.alpha. inserted within the recombinant PE molecule after about amino acid 607 and followed by amino acids 604-613 of domain III.

9. The recombinant PE molecule of claim 1, wherein the PE molecule includes an endoplasmic retention sequence at a carboxyl terminal end of the molecule.

10. The recombinant PE fusion protein of claim 1, wherein the molecule further comprises a substantial deletion of domain III.

11. The recombinant fusion protein of claim 10, wherein about amino acids 604 to 613 of domain III are retained.

12. The recombinant PE fusion protein of claim 11, wherein the ligand binding agent is fused to the PE in place of deleted domain III.

13. An isolated and purified recombinant Pseudomonas exotoxin (PE) fusion protein wherein a ligand binding agent is fused to a PE molecule in which:

(a) domain Ia is deleted;

(b) from 1 to 28 amino acids from the amino terminal end of domain II are deleted; and,

(c) a methionine residue is inserted at the resultant amino terminus of said molecule;

(d) wherein the fusion protein is further characterized in that it is at least twenty times more cytotoxic to target cells bound by the ligand binding agent in a cytotoxicity assay when compared with an unmodified PE40 fused to the ligand binding agent.

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L14: Entry 26 of 36 File: USPT Dec 24, 1996

US-PAT-NO: 5587455
DOCUMENT-IDENTIFIER: US 5587455 A

TITLE: Cytotoxic agent against specific virus infection

DATE-ISSUED: December 24, 1996

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Berger; Edward A.	Rockville	MD		
Moss; Bernard	Bethesda	MD		
Fuerst; Thomas R.	Gaithersburg	MD		
Pastan; Ira	Potomac	MD		
Fitzgerald; David	Rockville	MD		
Mizukami; Tamio	Machida			JP
Chaudhary; Vijay K.	New Delhi			IN

US-CL-CURRENT: 530/324; 530/350

CLAIMS:

What is claimed is:

1. A hybrid protein comprising a virus binding region from a cellular receptor sequence linked to a protein toxin sequence containing a region essential for cell toxicity, wherein said cellular receptor sequence is CD4.

2. The hybrid protein of claim 1 wherein the cellular receptor sequence is from CD4 and protein toxin sequence is from Pseudomonas exotoxin A.

3. A composition comprising the hybrid protein of claim 1 in an amount sufficient to kill a HIV-infected cell.

4. A hybrid protein according to claim 1 wherein the hybrid protein comprises a sequence of human CD4 containing a binding site for HIV linked to a cytotoxic protein, and wherein said hybrid protein binds to an HIV infected cell through said binding site, is internalized into and kills the HIV infected cell.

5. The hybrid protein of claim 2 wherein said protein is a recombinant fusion protein consisting of the first 178 amino acids of the CD4 cellular receptor and amino acids 1 to 3 and 253 to 613 of the Pseudomonas exotoxin A.

6. The composition of claim 3 further comprising a pharmaceutically acceptable, sterile, non-toxic carrier.

7. The hybrid protein according to claim 4 wherein the cytotoxic protein comprises a translocation and ADP-ribosylation domain.

8. The hybrid protein according to claim 4 wherein the cytotoxic protein is selected from the group consisting of Pseudomonas exotoxin A, diphtheria toxin fragment and ricin A.

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L14: Entry 4 of 36 File: USPT Oct 8, 2002

DOCUMENT-IDENTIFIER: US 6461617 B1
TITLE: Recombinant toxin fragments

CLAIMS:

1. A non-toxic polypeptide comprising first, second and third domains, wherein (a) said first domain comprises a botulinum toxin light chain and cleaves one or more vesicle or plasma-membrane associated proteins essential to exocytosis, (b) said second domain comprises the first 100 N-terminal amino acids of a botulinum toxin heavy chain and (i) translocates the polypeptide into a cell or (ii) increases the solubility of the polypeptide compared to the solubility of the first domain on its own or (iii) both translocates the polypeptide into a cell and increases the solubility of the polypeptide compared to the solubility of the first domain on its own, (c) said polypeptide is free of clostridial neurotoxin and free of clostridial neurotoxin precursor that can be converted into toxin by proteolytic action, (d) said polypeptide is a single polypeptide, (e) said third domain is a tandem repeat synthetic IgG binding domain derived from domain beta. of Staphylococcal protein A, and (f) said polypeptide lacks a portion designated H.sub.c of a botulinum toxin heavy chain.

2. A non-toxin polypeptide comprising first, second and third domains, wherein (a) said first domain comprises a botulinum toxin light chain and cleaves one or more vesicle or plasma-membrane associated proteins essential to exocytosis, (b) said second domain comprises the first 100 N-terminal amino acids of a botulinum toxin heavy chains and (i) translocates the polypeptide into a cell of (ii) increases the solubility of the polypeptide compared to the solubility of the first domain on its own or (iii) both translocates the polypeptide into a cell and increases the solubility of the polypeptide compared to the solubility of the first domain on its own, (c) said polypeptide is free of clostridial neurotoxin and free of clostridial neurotoxin precursor that can be converted into toxin by proteolytic action, (d) said polypeptide is a single polypeptide, (e) said third domain is insulin-like growth-factor-1 (IGF-1), and (f) said polypeptide lacks a portion designated H.sub.c of a botulinum toxin heavy chain.

3. A non-toxin polypeptide comprising first and second domains, wherein (a) said first domain is a botulinum toxin type A light chain variant comprising a sequence correspond to amino acids 1-448 of SEQ ID NO:2 wherein three amino acid residues have been altered compared to that sequence, namely at residue 2 a glutamate, at residue 26 a lysine and at residue 27 a tyrosine which first domain cleaves one or more vesicle or plasma-membrane associated proteins essential to exocytosis, (b) said second domain comprises the first 100 N-terminal amino acids of a botulinum toxin heavy chains and (i) translocates the polypeptide into a cell of (ii) increases the solubility of the polypeptide compared to the solubility of the first domain on its own or (iii) both translocates the polypeptide into a cell and increases the solubility of the polypeptide compared to the solubility of the first domain on its own, (c) said polypeptide is free of clostridial neurotoxin and free of clostridial neurotoxin precursor that can be converted into toxin by proteolytic action, (d) said polypeptide is a